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04105312.5

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R C van Dijk



Anmeldung Nr:
Application no.: 04105312.5
Demande no:

Anmeldetag:
Date of filing: 26.10.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

Tibotec Pharmaceuticals Ltd.
Little Island
Co Cork
IRLANDE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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MORPHOLINYL CONTAINING BENZIMIDAZOLES AS INHIBITORS OF RESPIRATORY SYNCYTIAL
VIRUS REPLICATION

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D413/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PL PT RO SE SI SK TR LI

MORPHOLINYL CONTAINING BENZIMIDAZOLES AS INHIBITORS OF RESPIRATORY SYNCYTIAL VIRUS REPLICATION

5 The present invention is concerned with morpholinyl containing benzimidazoles having antiviral activity, in particular, they have an inhibitory activity on the replication of the respiratory syncytial virus (RSV). It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

10 Human RSV or Respiratory Syncytial Virus is a large RNA virus, member of the family of Paramyxoviridae, subfamily pneumovirinae together with bovine RSV virus. Human RSV is responsible for a spectrum of respiratory tract diseases in people of all ages throughout the world. It is the major cause of lower respiratory tract illness during infancy and childhood. Over half of all infants encounter RSV in their first year of life, and almost all within their first two years. The infection in young children can cause
15 lung damage that persists for years and may contribute to chronic lung disease in later life (chronic wheezing, asthma). Older children and adults often suffer from a (bad) common cold upon RSV infection. In old age, susceptibility again increases, and RSV has been implicated in a number of outbreaks of pneumonia in the aged resulting in significant mortality.

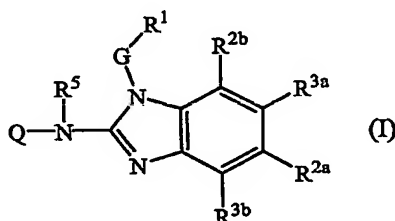
20 Infection with a virus from a given subgroup does not protect against a subsequent infection with an RSV isolate from the same subgroup in the following winter season. Re-infection with RSV is thus common, despite the existence of only two subtypes, A and B.

25 Today only three drugs have been approved for use against RSV infection. A first one is ribavirin, a nucleoside analogue, provides an aerosol treatment for serious RSV infection in hospitalized children. The aerosol route of administration, the toxicity (risk of teratogenicity), the cost and the highly variable efficacy limit its use. The other two
30 drugs, RespiGam[®] and palivizumab, polyclonal and monoclonal antibody immunostimulants, are intended to be used in a preventive way.

35 Other attempts to develop a safe and effective RSV vaccine have all met with failure thus far. Inactivated vaccines failed to protect against disease, and in fact in some cases enhanced disease during subsequent infection. Live attenuated vaccines have been tried with limited success. Clearly there is a need for an efficacious non-toxic and easy to administer drug against RSV replication.

Previously, benzimidazoles and imidazopyridines as inhibitors of RSV replication have been described in WO 01/00611, WO 01/00612 and WO 01/00615.

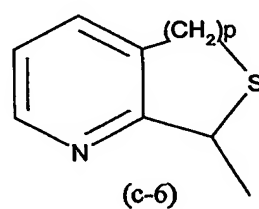
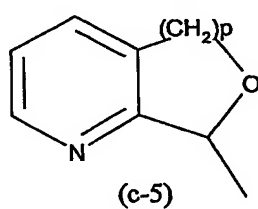
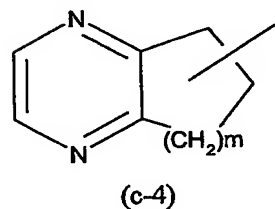
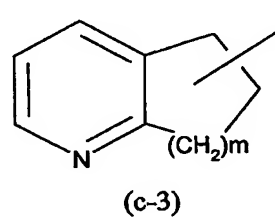
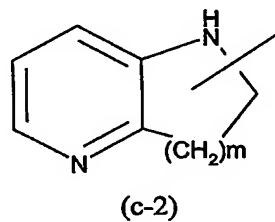
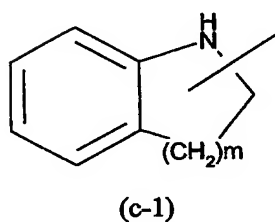
The present invention now concerns inhibitors of RSV replication and are defined as the compounds of formula (I)

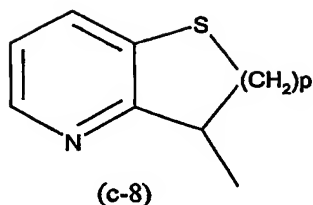
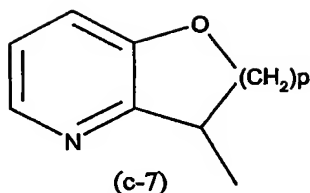


their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms wherein

G is a direct bond or C₁₋₁₀alkanediyl optionally substituted with one or more substituents individually selected from the group of substituents consisting of hydroxy, C₁₋₆alkyloxy, Ar¹C₁₋₆alkyloxy, C₁₋₆alkylthio, Ar¹C₁₋₆alkylthio, HO(-CH₂-CH₂-O)_n, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n or Ar¹C₁₋₆alkyloxy(-CH₂-CH₂-O)_n;

R¹ is Ar¹ or a monocyclic or bicyclic heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranlyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, quinolinyl, quinoxalinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-*b*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridyl or a radical of formula





;

- wherein each of said monocyclic or bicyclic heterocycles may optionally be substituted with 1 or where possible more, such as 2, 3, 4 or 5, substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, Ar¹, Ar¹C₁₋₆alkyl, Ar¹C₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)amino, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, Ar¹-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, Ar¹C₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono- or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-; each n independently is 1, 2, 3 or 4; each m independently is 1 or 2; each p independently is 1 or 2; each t independently is 0, 1 or 2;
- Q is R⁷, pyrrolidinyl substituted with R⁷, piperidinyl substituted with R⁷ or homo-piperidinyl substituted with R⁷ wherein R⁷ is C₁₋₆alkyl substituted with a heterocycle or R⁷ is C₁₋₆alkyl substituted with both a radical -OR⁸ and a heterocycle, wherein said heterocycle is selected from the group consisting of oxazolidine, thiazolidine, 1-oxo-thiazolidine, 1,1-dioxothiazolidine, morpholinyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxothiomorpholinyl, hexahydrooxazepine, hexahydrothiazepine, 1-oxo-hexahydrothiazepine, 1,1-dioxo-hexahydrothiazepine; wherein each of said heterocycle may be optionally substituted with one or two substituents selected from the group consisting of C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, hydroxy, carboxyl, C₁₋₄alkyloxycarbonyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, C₁₋₄alkylcarbonylamino, aminosulfonyl and mono- or di(C₁₋₄alkyl)aminosulfonyl; R⁸ is hydrogen, C₁₋₆alkyl or Ar¹C₁₋₆alkyl; one of R^{2a} and R^{3a} is selected from halo, optionally mono- or polysubstituted C₁₋₆alkyl, optionally mono- or polysubstituted C₂₋₆alkenyl, nitro, hydroxy, Ar², N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, N(R^{4a}R^{4b})carbonyl, C₁₋₆alkyloxy, Ar²oxy, Ar²C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, or -C(=Z)Ar²; and the other one of R^{2a} and R^{3a} is hydrogen; wherein

- $=Z$ is $=O$, $=CH-C(=O)-NR^{5a}R^{5b}$, $=CH_2$, $=CH-C_{1-6}alkyl$, $=N-OH$ or $=N-O-C_{1-6}alkyl$; and
 - the optional substituents on $C_{1-6}alkyl$ and $C_{2-6}alkenyl$ can be the same or can be different relative to one another, and are each independently selected from the group of substituents consisting of hydroxy, cyano, halo, nitro, $N(R^{4a}R^{4b})$, $N(R^{4a}R^{4b})sulfonyl$, Het, Ar^2 , $C_{1-6}alkyloxy$, $C_{1-6}alkyl-S(=O)_t$, Ar^2oxy , $Ar^2-S(=O)_t$, $Ar^2C_{1-6}alkyloxy$, $Ar^2C_{1-6}alkyl-S(=O)_t$, Het-oxy, Het-S(=O)_t, Het $C_{1-6}alkyloxy$, Het $C_{1-6}alkyl-S(=O)_t$, carboxyl, $C_{1-6}alkyloxycarbonyl$ and $-C(=Z)Ar^2$;
- 5 in case R^{2a} is different from hydrogen then R^{2b} is hydrogen, $C_{1-6}alkyl$ or halogen and R^{3b} is hydrogen;
- in case R^{3a} is different from hydrogen then R^{3b} is hydrogen, $C_{1-6}alkyl$ or halogen and R^{2b} is hydrogen;
- R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each
- 15 independently selected from the group of substituents consisting of hydrogen, $C_{1-6}alkyl$, $Ar^2C_{1-6}alkyl$, Het- $C_{1-6}alkyl$, $C_{1-6}alkyloxyC_{1-6}alkyl$, amino $C_{1-6}alkyl$, mono- or di($C_{1-6}alkyl$)amino $C_{1-6}alkyl$, hydroxy $C_{1-6}alkyl$, carboxyl $C_{1-6}alkyl$, $C_{1-6}alkyloxycarbonylC_{1-6}alkyl$, aminocarbonyl $C_{1-6}alkyl$, mono- and di($C_{1-6}alkyl$)aminocarbonyl $C_{1-6}alkyl$, $C_{1-6}alkylcarbonylC_{1-6}alkyl$, di($C_{1-6}alkyl$ -oxy)phosphonyl- $C_{1-6}alkyl$, $C_{1-6}alkylcarbonyl$, $Ar^2carbonyl$, Het-carbonyl, $Ar^2C_{1-6}alkylcarbonyl$, Het- $C_{1-6}alkylcarbonyl$, $C_{1-6}alkylsulfonyl$, aminosulfonyl, mono- and di($C_{1-6}alkyl$)aminosulfonyl, $Ar^2sulfonyl$, $Ar^2C_{1-6}alkylsulfonyl$, Ar^2 , Het, Het-sulfonyl, Het $C_{1-6}alkylsulfonyl$; ; R^5 is hydrogen or $C_{1-6}alkyl$;
- 20 R^{5a} and R^{5b} can be the same or can be different relative to one another, and are each
- 25 independently hydrogen or $C_{1-6}alkyl$; or
- R^{5a} and R^{5b} taken together may form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
- R^{5c} and R^{5d} can be the same or can be different relative to one another, and are each independently hydrogen or $C_{1-6}alkyl$; or
- 30 R^{5c} and R^{5d} taken together may form a bivalent radical of formula $-(CH_2)_s-$ wherein s is 4 or 5;
- Ar^1 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, $C_{1-6}alkyl$, hydroxy $C_{1-6}alkyl$, polyhalo $C_{1-6}alkyl$, and $C_{1-6}alkyloxy$;
- 35 Ar^2 is phenyl, phenyl annelated with a $C_{5-7}cycloalkyl$, or phenyl substituted with 1 or more, such as 2, 3, 4 or 5, substituents selected from halo, cyano, $C_{1-6}alkyl$, Het- $C_{1-6}alkyl$, $Ar^1-C_{1-6}alkyl$, cyano $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, cyano- $C_{2-6}alkenyl$, Ar^1 , $R^{6b}-O-$, $R^{6b}-S-$, $R^{6c}-SO-$, $R^{6c}-SO_2-$, $-N(R^{6a}R^{6b})$, polyhalo-

5 C₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, polyhaloC₁₋₆alkylthio, R^{6c}-C(=O)-, R^{6b}-O-C(=O)-, N(R^{6a}R^{6b})-C(=O)-, R^{6b}-O-C₁₋₆alkyl, R^{6b}-S-C₁₋₆alkyl, R^{6c}-S(=O)₂-C₁₋₆alkyl, N(R^{6a}R^{6b})-C₁₋₆alkyl, R^{6c}-C(=O)-C₁₋₆alkyl, R^{6b}-O-C(=O)-C₁₋₆alkyl, N(R^{6a}R^{6b})-C(=O)-C₁₋₆alkyl, R^{6c}-C(=O)-NR^{6b}-, R^{6c}-C(=O)-O-, R^{6c}-C(=O)-NR^{6b}-C₁₋₆alkyl, R^{6c}-C(=O)-O-C₁₋₆alkyl, N(R^{6a}R^{6b})-S(=O)₂-;

10 R^{6a} is hydrogen, C₁₋₆alkyl, Ar¹, Ar¹C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹carbonyl, Ar¹C₁₋₆alkylcarbonyl, C₁₋₆alkylsulfonyl, Ar¹sulfonyl, Ar¹C₁₋₆alkylsulfonyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, Het, Het-C₁₋₆alkyl, Het-carbonyl, Het-sulfonyl, Het-C₁₋₆alkylcarbonyl;

R^{6b} is hydrogen, C₁₋₆alkyl, Ar¹ or Ar¹C₁₋₆alkyl;

R^{6c} is C₁₋₆alkyl, Ar¹ or Ar¹C₁₋₆alkyl;

15 Het is a heterocycle being selected from tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidinonyl, furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzodioxolyl, indolinyl, indolyl, each of said heterocycle may
20 optionally be substituted with oxo, amino, Ar¹, C₁₋₄alkyl, aminoC₁₋₄alkyl, Ar¹C₁₋₄alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)amino.

The term prodrug as used throughout this text means the pharmacologically acceptable derivatives, e.g. esters and amides, such that the resulting biotransformation product of
25 the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p. 13-15) describing prodrugs generally, is hereby incorporated. Prodrugs are characterized by a good aqueous solubility and bioavailability, and are readily metabolized into the active
30 inhibitors *in vivo*.

The term 'polysubstituted C₁₋₆alkyl' or 'polysubstituted C₂₋₆alkenyl' such as used in the definition of R^{2a} and R^{3a} is meant to comprise C₁₋₆alkyl or C₂₋₆alkenyl radicals having two or more substituents, for example two, three, four, five or six substituents, in
35 particular two or three substituents. The upper limit of the number of substituents is determined by the number of hydrogen atoms that can be replaced as well as by the general properties of the substituents such as their bulkiness, these properties allowing the skilled person to determine said upper limit.

As used herein C₁₋₃alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl and the like; C₁₋₄alkyl as a group or part of a group defines
5 straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the group defined for C₁₋₃alkyl and butyl and the like; C₂₋₄alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 2 to 4 carbon atoms such as ethyl, propyl, 1-methylethyl, butyl and the like; C₁₋₆alkyl as a group or part of a group defines straight or branched chain
10 saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for C₁₋₄alkyl and pentyl, hexyl, 2-methylbutyl and the like; C₁₋₉alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 9 carbon atoms such as the groups defined for C₁₋₆alkyl and heptyl, octyl, nonyl, 2-methylhexyl, 2-methylheptyl and the like; C₁₋₁₀alkyl as a group or part
15 of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C₁₋₉alkyl and decyl, 2-methylnonyl and the like.

C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and
20 cycloheptyl.

C₂₋₅alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 2 to 5 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediy
25 the like, C₁₋₄alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C₁₋₆alkanediyl is meant to include C₁₋₄alkanediyl and the higher homologues thereof having from 5 to 6 carbon atoms such as, for example, 1,5-pentanediy
30 C₁₋₁₀alkanediyl is meant to include C₁₋₆alkanediyl and the higher homologues thereof having from 7 to 10 carbon atoms such as, for example, 1,7-heptanediy, 1,8-octanediy, 1,9-nonanediy, 1,10-decanediyl and the like.

As used herein the term 'R⁷ is C₁₋₆alkyl substituted with both a radical -OR⁸ and a
35 heterocycle' refers to a C₁₋₆alkyl radical bearing two substituents, i.e. the group -OR⁸ and a heterocycle and linked to the rest of the molecule through a carbon atom of the C₁₋₆alkyl moiety. Preferably the -OR⁸ group is linked to a carbon atom of the C₁₋₆alkyl moiety that is not adjacent (not in α -position) to a heteroatom (such as a nitrogen

atom). More preferably the radical R^7 being C_{1-6} alkyl substituted with both a radical $-OR^8$ and a heterocycle' is a radical that can be represented by the formula $-CH_2-CH(OR^8)-CH_2-$.

- 5 The heterocycle in R^7 preferably is linked to the group C_{1-6} alkyl via its nitrogen atom. The radicals hexahydrooxazepine, hexahydrothiazepine, 1-oxo-hexahydrothiazepine and 1,1-dioxo-hexahydrothiazepine preferably are 1,4-hexahydrooxazepine, 1,4-hexahydrothiazepine, 1-oxo-1,4-hexahydrothiazepine and 1,1-dioxo-1,4-hexahydrothiazepine.

10

As used herein before, the term $(=O)$ forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. The term $(=N-OH)$ forms a hydroxyimine moiety when attached to a carbon atom.

15

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalo C_{1-6} alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6} alkyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl. In case more than one halogen atom is attached to an alkyl group within the definition of polyhalo C_{1-4} alkyl, the halogen atoms may be the same or different.

20

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

25

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

- 30 When any variable occurs more than one time in any constituent, each definition is independent.

35

Whenever used hereinafter, the term "compounds of formula (I)", or "the present compounds" or similar term is meant to include the compounds of general formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms. An interesting subgroup of the compounds of formula (I) or any subgroup thereof are the *N*-oxides, salts and all the stereoisomeric forms of the compounds of formula (I).

It will be appreciated that some of the compounds of formula (I) may contain one or more centers of chirality and exist as stereochemically isomeric forms.

5 The term "stereochemically isomeric forms" as used hereinbefore defines all the possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess.

10 Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

15 Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a
20 stereoisomeric excess of at least 80% (i. e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a
25 stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, respectively the diastereomeric excess of the mixture in question.

30 Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyl-tartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers
35 may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said

compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

5 The diastereomeric racemates of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

10 For some of the compounds of formula (I), their prodrugs, N-oxides, salts, solvates, quaternary amines, or metal complexes and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

15 The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

20 For therapeutic use, salts of the compounds of formula (I) are those wherein the counter-ion is pharmaceutically acceptable. However, salts of acids and bases, which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

25 The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form
30 with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric,
35 methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into
40 the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates, which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkyl halide, aryl halide or arylalkyl halide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethane sulfonates, alkyl methane sulfonates, and alkyl *p*-toluenesulfonates. A quaternary amine has a positively charged nitrogen.

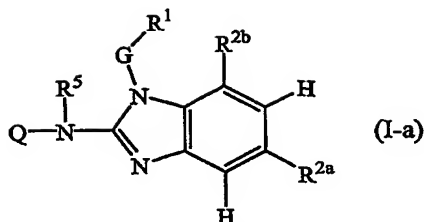
Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complexing properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

One embodiment of the present invention concerns compounds of formula (I-a):



wherein Q, R⁵, G and R¹ are as specified above and

R^{2a} is selected from halo, optionally mono- or polysubstituted C₁₋₆alkyl, optionally mono- or polysubstituted C₂₋₆alkenyl, nitro, hydroxy, Ar², N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, N(R^{4a}R^{4b})carbonyl, C₁₋₆alkyloxy, Ar²oxy, Ar²C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, or -C(=Z)Ar²;

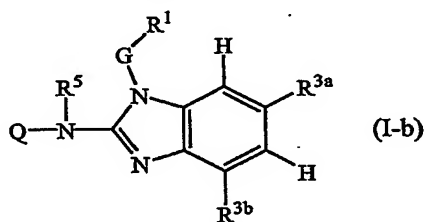
wherein

- =Z is =O, =CH-C(=O)-NR^{5a}R^{5b}, =CH₂, =CH-C₁₋₆alkyl, =N-OH or =N-O-C₁₋₆alkyl; and

- the optional substituents on C₁₋₆alkyl and C₂₋₆alkenyl can be the same or can be different relative to one another, and are each independently selected from the group of substituents consisting of hydroxy, cyano, halo, nitro, N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, Het, Ar², C₁₋₆alkyloxy, C₁₋₆alkyl-S(=O)_t, Ar²oxy, Ar²-S(=O)_t, Ar²C₁₋₆alkyloxy, Ar²C₁₋₆alkyl-S(=O)_t, Het-oxy, Het-S(=O)_t, HetC₁₋₆alkyloxy, HetC₁₋₆alkyl-S(=O)_t, carboxyl, C₁₋₆alkyloxycarbonyl and -C(=Z)Ar²;

R^{2b} is hydrogen, C₁₋₆alkyl or halogen.

Another embodiment of the present invention concerns compounds of formula (I-b):



wherein Q, R⁵, G and R¹ are as specified above and

R^{3a} is selected from halo, optionally mono- or polysubstituted C₁₋₆alkyl, optionally mono- or polysubstituted C₂₋₆alkenyl, nitro, hydroxy, Ar², N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, N(R^{4a}R^{4b})carbonyl, C₁₋₆alkyloxy, Ar²oxy, Ar²C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, or -C(=Z)Ar²;

wherein

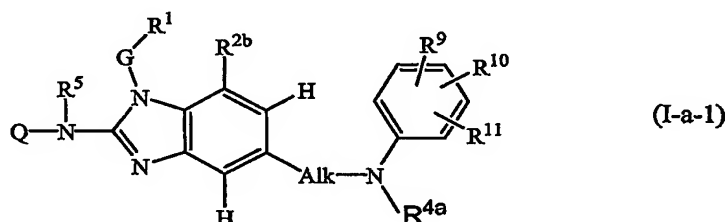
- =Z is =O, =CH-C(=O)-NR^{5a}R^{5b}, =CH₂, =CH-C₁₋₆alkyl, =N-OH or =N-O-C₁₋₆alkyl; and

- the optional substituents on C₁₋₆alkyl and C₂₋₆alkenyl can be the same or can be different relative to one another, and are each independently selected from

the group of substituents consisting of hydroxy, cyano, halo, nitro, $N(R^{4a}R^{4b})$, $N(R^{4a}R^{4b})$ sulfonyl, Het, Ar^2 , C_{1-6} alkyloxy, C_{1-6} alkyl-S(=O)_t, Ar^2 oxy, Ar^2 -S(=O)_t, Ar^2C_{1-6} alkyloxy, Ar^2C_{1-6} alkyl-S(=O)_t, Het-oxy, Het-S(=O)_t, Het C_{1-6} alkyloxy, Het C_{1-6} alkyl-S(=O)_t, carboxyl, C_{1-6} alkyloxycarbonyl and $-C(=Z)Ar^2$;

R^{3b} is hydrogen, C_{1-6} alkyl or halogen.

One particular embodiment of the present invention concerns compounds of formula (I-a-1):

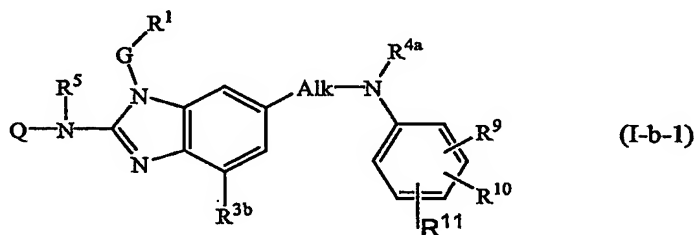


wherein Q, R^5 , G and R^{4a} are as specified above and Alk is C_{1-6} alkanediyl;

R^9 , R^{10} , R^{11} independently from one another are halo, cyano, C_{1-6} alkyl, Het- C_{1-6} alkyl, Ar^1 - C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cyano C_{2-6} alkenyl, Ar^1 , R^{6b} -O-, R^{6b} -S-, R^{6c} -SO-, R^{6c} -SO₂-, $-N(R^{6a}R^{6b})$, polyhalo C_{1-6} alkyl, polyhalo- C_{1-6} alkyloxy, polyhalo C_{1-6} alkylthio, R^{6c} -C(=O)-, R^{6b} -O-C(=O)-, $N(R^{6a}R^{6b})$ -C(=O)-, R^{6b} -O- C_{1-6} alkyl, R^{6b} -S- C_{1-6} alkyl, R^{6c} -S(=O)₂- C_{1-6} alkyl, $N(R^{6a}R^{6b})$ - C_{1-6} alkyl, R^{6c} -C(=O)- C_{1-6} alkyl, R^{6b} -O-C(=O)- C_{1-6} alkyl, $N(R^{6a}R^{6b})$ -C(=O)- C_{1-6} alkyl, R^{6c} -C(=O)-NR^{6b}-, R^{6c} -C(=O)-O-, R^{6c} -C(=O)-NR^{6b}- C_{1-6} alkyl, R^{6c} -C(=O)-O- C_{1-6} alkyl, $N(R^{6a}R^{6b})$ -S(=O)₂-; and R^{10} and/or R^{11} may also be hydrogen.

R^{2b} is hydrogen, C_{1-6} alkyl or halogen.

Another particular embodiment of the present invention concerns compounds of formula (I-b):



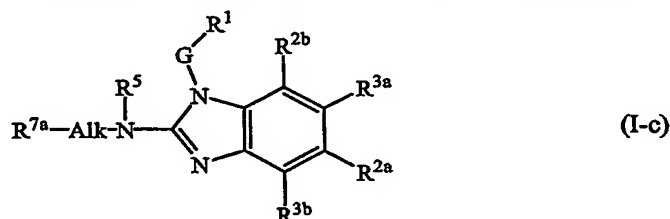
wherein Q, R^5 , G, R^1 , and R^{4a} are as specified above and Alk is C_{1-6} alkanediyl;

R^9 , R^{10} , R^{11} independently from one another are halo, cyano, C_{1-6} alkyl, Het- C_{1-6} alkyl, Ar^1 - C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, cyano C_{2-6} alkenyl, Ar^1 ,

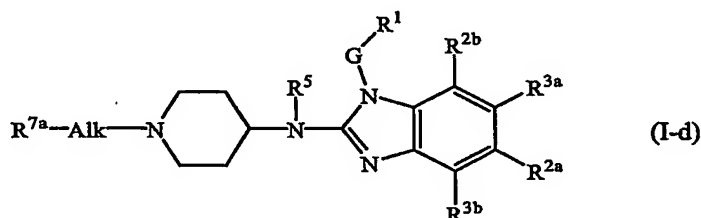
- 5 R^{6b} -O-, R^{6b} -S-, R^{6c} -SO-, R^{6c} -SO₂-, -N(R^{6a} R^{6b}), polyhaloC₁₋₆alkyl, polyhaloC₁₋₆alkyloxy, polyhaloC₁₋₆alkylthio, R^{6c} -C(=O)-, R^{6b} -O-C(=O)-, N(R^{6a} R^{6b})-C(=O)-, R^{6b} -O-C₁₋₆alkyl, R^{6b} -S-C₁₋₆alkyl, R^{6c} -S(=O)₂-C₁₋₆alkyl, N(R^{6a} R^{6b})-C₁₋₆alkyl, R^{6c} -C(=O)-C₁₋₆alkyl, R^{6b} -O-C(=O)-C₁₋₆alkyl, N(R^{6a} R^{6b})-C(=O)-C₁₋₆alkyl, R^{6c} -C(=O)-NR^{6b}-, R^{6c} -C(=O)-O-, R^{6c} -C(=O)-NR^{6b}-C₁₋₆alkyl, R^{6c} -C(=O)-O-C₁₋₆alkyl, N(R^{6a} R^{6b})-S(=O)₂-; and R¹⁰ and/or R¹¹ may also be hydrogen.

R^{3b} is hydrogen, C₁₋₆alkyl or halogen.

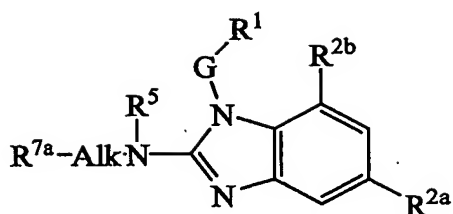
- 10 Still another embodiments are compounds which can be represented by formula



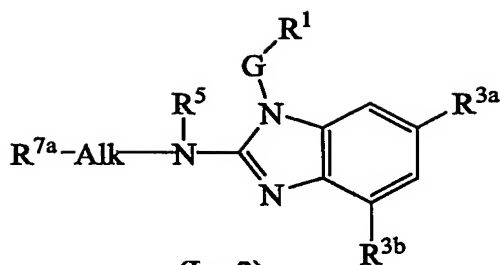
or by formula



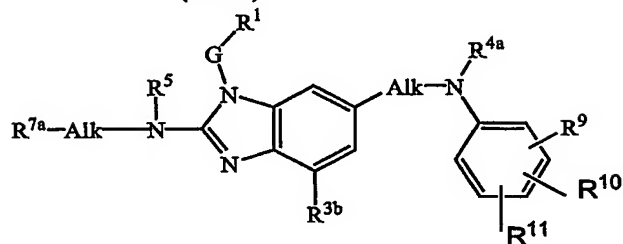
- wherein in (I-c) or (I-d) R⁵, G, R¹, R^{2a}, R^{2b}, R^{3a}, R^{3b} are as specified above and
- 15 Alk is C₁₋₆alkanediyl;
- R^{7a} is a heterocycle which is selected from the group consisting of oxazolidine, thiazolidine, 1-oxo-thiazolidine, 1,1-dioxothiazolidine, morpholinyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxothiomorpholinyl, hexahydrooxazepine, hexahydrothiazepine, 1-oxo-hexahydrothiazepine and 1,1-dioxohexahydrothiazepine;
- 20 wherein each of said heterocycle may be optionally substituted with one or two substituents selected from the group consisting of C₁₋₆alkyl, hydroxy, carboxyl, C₁₋₄alkyloxycarbonyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, C₁₋₄alkylcarbonylamino, aminosulfonyl and mono- or di(C₁₋₄alkyl)aminosulfonyl.
- 25 Of interest are compounds of formulas



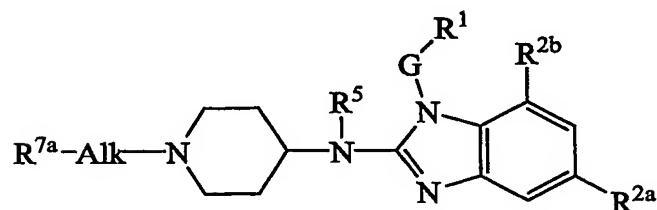
(I-c-1)



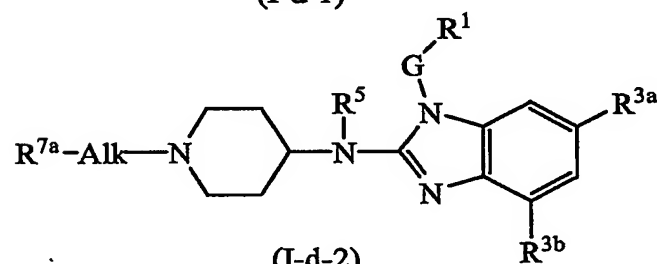
(I-c-2)



(I-c-3)



(I-d-1)



(I-d-2)

- 5 wherein in (I-c-1), (I-c-2), (I-c-3), (I-d-1) or (I-d-2) R^5 , G , R^1 , R^{2a} , R^{2b} , R^{3a} , R^{3b} , R^9 , R^{10} , R^{11} are as specified above and
Alk is C_{1-6} alkanediyl;
 R^{7a} is a heterocycle, wherein said heterocycle is selected from the group consisting of
10 oxazolidine, thiazolidine, 1-oxo-thiazolidine, 1,1-dioxothiazolidine, morpholinyl,
thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxothiomorpholinyl, hexahydro-
oxazepine, hexahydrothiazepine, 1-oxo-hexahydrothiazepine, 1,1-dioxo-hexahydro-
thiazepine; wherein each of said heterocycle may be optionally substituted with one or
two substituents selected from the group consisting of C_{1-6} alkyl, hydroxy, carboxyl,
 C_{1-4} alkyloxycarbonyl, aminocarbonyl, mono- or di(C_{1-4} alkyl)aminocarbonyl,
15 C_{1-4} alkylcarbonylamino, aminosulfonyl and mono- or di(C_{1-4} alkyl)aminosulfonyl.
 R^{7a} preferably is morpholinyl, thiomorpholinyl, 1-oxo-thiomorpholinyl,
1,1-dioxothiomorpholinyl, hexahydrooxazepine, hexahydrothiazepine, 1-oxo-
hexahydrothiazepine, 1,1-dioxo-hexahydrothiazepine; wherein each of said heterocycle

may be optionally substituted with one or two substituents selected from the group consisting of C₁₋₆alkyl, carboxyl, C₁₋₄alkyloxycarbonyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, aminosulfonyl and mono- or di(C₁₋₄alkyl)aminosulfonyl.

5 R^{7a} more preferably is morpholinyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxothiomorpholinyl, hexahydrooxazepine, hexahydrothiazepine, 1-oxo-hexahydrothiazepine, 1,1-dioxo-hexahydrothiazepine; wherein each of said heterocycle may be optionally substituted with one or two substituents selected from the group consisting of C₁₋₆alkyl.

10 R^{7a} still more preferably is morpholinyl, thiomorpholinyl, hexahydrooxazepine, hexahydrothiazepine, wherein each of said heterocycle may be optionally substituted with one or two substituents selected from the group consisting of C₁₋₆alkyl.

R^{7a} still more preferably is morpholinyl.

Alk preferably is methylene.

15 R^{4a} preferably is hydrogen or C₁₋₆alkyl; R^{4a} more preferably is hydrogen.

R⁹, R¹⁰, R¹¹ preferably and independently from one another are C₁₋₆alkyl or R^{6b}-O-C₁₋₆alkyl; and R¹⁰ and/or R¹¹ may also be hydrogen.

R⁹, R¹⁰ more preferably and independently from one another are C₁₋₆alkyl or R^{6b}-O-C₁₋₆alkyl; and R¹¹ is hydrogen.

20 R⁹, R¹⁰ still more preferably are C₁₋₆alkyl and R¹¹ is hydrogen; or R⁹ is C₁₋₆alkyl, R¹⁰ is R^{6b}-O-C₁₋₆alkyl and R¹¹ is hydrogen.

25 It is to be understood that the above defined subgroups of compounds of formulae (I-a), (I-b), etc. as well as any other subgroup defined herein are also meant to comprise any prodrugs, N-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms of such compounds.

30 Interesting compounds are those compounds of formula (I) or any subgroup thereof wherein G is C₁₋₁₀alkanediyl; more in particular, wherein G is methylene.

Other interesting compounds are those compounds of formula (I) or any subgroup thereof wherein

35 R¹ is Ar¹ or a monocyclic heterocycle, which are defined above or below; or R¹ is pyridyl optionally substituted with 1 or 2 substituents independently selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, Ar¹, Ar¹C₁₋₆alkyl, Ar¹C₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)amino, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, Ar¹-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d},

HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-,
Ar¹C₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-; more
in particular

- 5 R¹ is pyridyl substituted with with 1 or 2 substituents independently selected from the
group of substituents consisting of hydroxy and C₁₋₆alkyl; or
R¹ is pyridyl substituted with hydroxy and C₁₋₆alkyl.

R⁵ preferably is hydrogen.

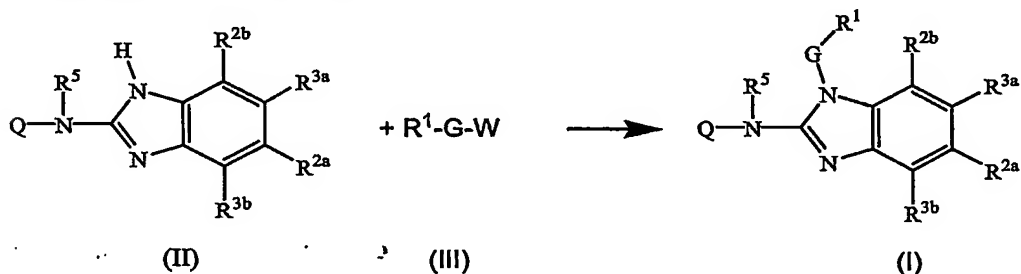
- 10 R⁷ preferably is C₁₋₆alkyl substituted with a radical R^{7a} wherein the latter is as specified
above.

Alk preferably is methylene.

Other interesting compounds are those compounds of formula (I) wherein t is 2.

- 15 Preferred compounds are those compounds listed in tables 1 through 8, more in
particular the compound numbers 1 to 24, 26 to 77, 80 to 83, 90 to 92, 97 and 99.

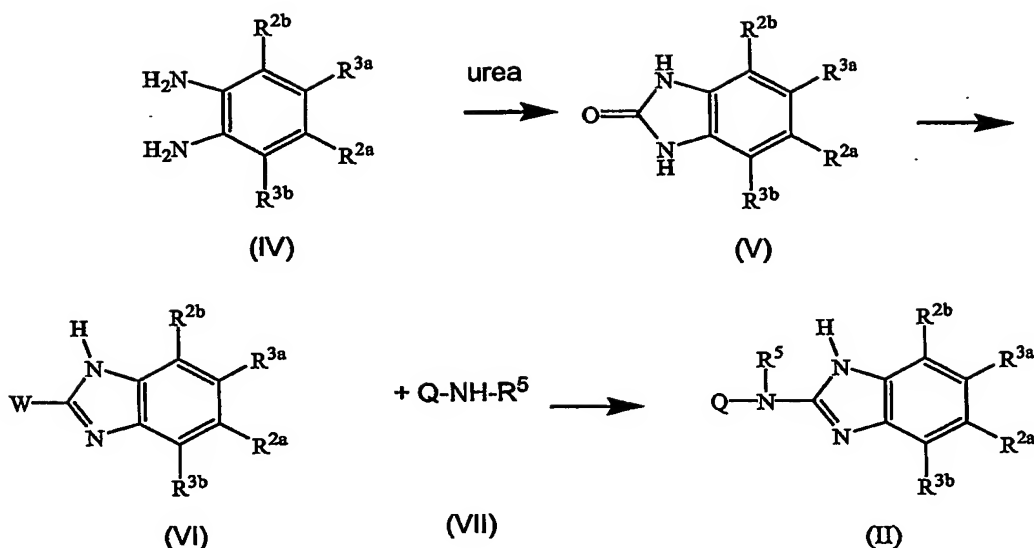
The compounds of formula (I) or any of the subgroups thereof can be prepared as in the
following reaction schemes.



- 20 In this schemes Q, G, R¹, R^{2a}, R^{2b}, R^{3a}, R^{3b} R⁵ have the meanings defined above for
the compounds of formula (I) or of any of the subgroups thereof. W is an appropriate
leaving group, preferably it is chloro or bromo. The reaction of this scheme is typically
conducted in a suitable solvent such as an ether, e.g. THF, a halogenated hydrocarbon,
e.g. dichloromethane, CHCl₃, toluene, a polar aprotic solvent such as DMF, DMSO,
25 DMA and the like.

Compounds of formula (I) may be converted into each other following art-known
functional group transformation reactions, comprising those described hereinafter.

- 30 A number of the intermediates used to prepare the compounds of formula (I) are known
compounds or are analogs of known compounds which can be prepared following
modifications of art-known methodologies readily accessible to the skilled person. A
number of preparations of intermediates are given hereafter in somewhat more detail.



- In a first step, a diaminobenzene (IV) is cyclized with urea in a suitable solvent, e.g. xylene, to yield a benzimidazolone (V). The latter is converted to a benzimidazole derivative (VI) wherein W is a leaving group as specified above, in particular by reaction of (V) with a suitable halogenating agent, for example POCl₃, and the resulting intermediate (VI) is reacted with the amine derivative (VII) to obtain intermediate (II).
- The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboxylic acid or halo substituted benzenecarboxylic acid, e.g. 3-chlorobenzenecarboxylic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. t-butyl hydroperoxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) which are sufficiently basic or acidic may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I) show antiviral properties. Viral infections treatable using the compounds and methods of the present invention include those infections brought on by ortho- and paramyxoviruses and in particular by human and bovine respiratory syncytial virus (RSV).

The *in vitro* antiviral activity against RSV of the present compounds was tested in a test as described in the experimental part of the description, and may also be demonstrated in a virus yield reduction assay. The *in vivo* antiviral activity against RSV of the present compounds may be demonstrated in a test model using cotton rats as described in Wyde et al. (Antiviral Research (1998), 38, 31-42).

Due to their antiviral properties, particularly their anti-RSV properties, the compounds of formula (I) or any subgroup thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a RSV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular the respiratory syncytial virus.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the RSV infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly RSV infection.

5

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

35

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry

powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. Preferably, the compounds of the present invention are administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

In general it is contemplated that an antivirally effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

Also, the combination of another antiviral agent and a compound of formula (I) can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I), and (b) another antiviral compound, as a combined preparation for simultaneous, separate or sequential use in antiviral treatment. The

different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers. For instance, the compounds of the present invention may be combined with interferon-beta or tumor necrosis factor-alpha in order to treat or prevent RSV infections.

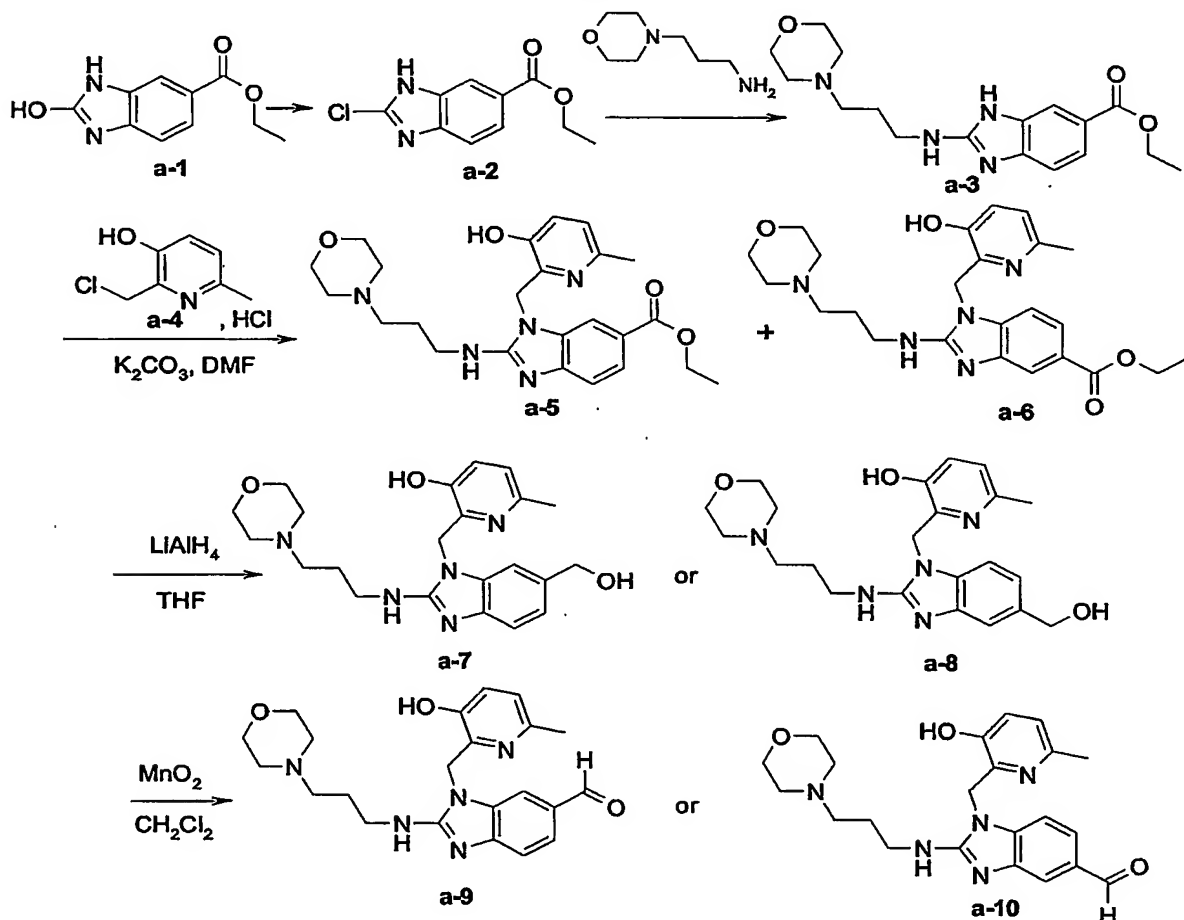
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Experimental Part

The following examples are intended to illustrate the present invention.

A. Chemical synthesis of the compounds of formula (I)

Scheme A-1



10

A mixture of 3,4-diamino benzoic acid ethyl ester (0.166 mol) and urea (0.199 mol) in xylene (300 ml) was stirred under reflux for 12 hours. The reaction was cooled down to room temperature. The precipitate was filtered off, rinsed with xylene and diisopropyl-ether, and then dried, yielding 32g of intermediate a-1 (93%, melting point: $> 260^\circ C$).

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A mixture of a-1 (0.073 mol) in $POCl_3$ (150 ml) was stirred at $100^\circ C$. HCl conc. (around 1.5 ml) was added drop wise very carefully until the dissolution of a-1. The mixture was stirred at $120^\circ C$ for 6 hours. The solvent was evaporated till dryness. The

residue was taken-up in H₂O/ice, basified with K₂CO₃ (powder) and extracted with ethylacetate + 10% methanol. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness, yielding 13.5 g of intermediate **a-2** (83%, melting point: 178°C).

5

A mixture of **a-2** (0.0356 mol) and N-propylamino-morpholine (0.0427 mol) was stirred at 120°C for 4 hours, and then taken up in CH₂Cl₂/CH₃OH. The organic layer was washed with a 10% solution of K₂CO₃ in water, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue (11.9g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 94/6/0.2; 15-40µm). The pure fractions were collected and the solvent was evaporated, yielding 6g of intermediate **a-3** (47%).

10

A mixture of **a-3** (0.018 mol), **a-4** (0.027 mol) and K₂CO₃ (0.054 mol) in CH₃CN (100ml) and dimethylformamide (10ml) was stirred at 80°C for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH₂Cl₂/H₂O. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was crystallized from 2-propanone. The precipitate was filtered, washed with H₂O and dried, yielding 2.8g of intermediate **a-6** (34%, melting point: 176°C). The mother layer was evaporated till dryness and purified by chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 93/7/0.7; 15-40µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN/diisopropylether, yielding 1.6g of intermediate **a-5** (20%, melting point: 184°C).

20
25

A mixture of **a-5** (0.0035 mol) in tetrahydrofuran (60ml) was cooled down to 5°C under N₂ flow. LiAlH₄ (0.0105 mol) was added portion wise. The mixture was stirred at 5°C for 1 hour, and then stirred at room temperature for 2 hours. A minimum of H₂O was added. CH₂Cl₂ was added. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 1.2g of intermediate **a-7** (83%). Part of this fraction (0.1g) was crystallized from 2-propanone/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.074g (melting point: 192°C). Intermediate **a-8** (melting point: 134°C) was prepared in an analogous way.

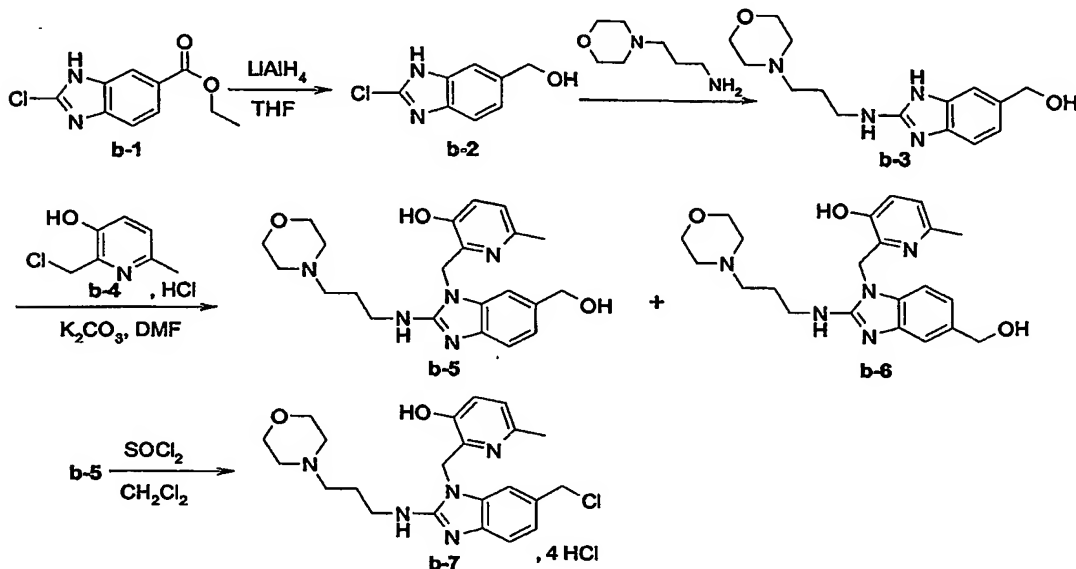
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35

A mixture of **a-7** (0.0024 mol) and MnO₂ (2g) in CH₂Cl₂ (50ml) was stirred at room temperature for 12 hours, and then filtered over celite. Celite was washed with H₂O.

The solvent of the filtrate was evaporated till dryness, yielding 0.9g of intermediate **a-9** (90%, melting point: 206°C). Intermediate **a-10** was prepared in an analogous way.

Scheme B



- 5 LiAlH_4 (0.146 mol) was added portion wise to a solution of tetrahydrofuran (200 ml) at 5°C under N_2 flow. A solution of **b-1** (0.073 mol) in tetrahydrofuran (200 ml) was then added drop wise. The mixture was stirred at 5°C for 3 hours. A minimum of H_2O was then added, followed by a solution of $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (90/10). The resulting mixture was dried (over MgSO_4), filtered and the solvent was evaporated till dryness, yielding
- 10 12.6g of intermediate **b-2** (95%, melting point: 179°C).

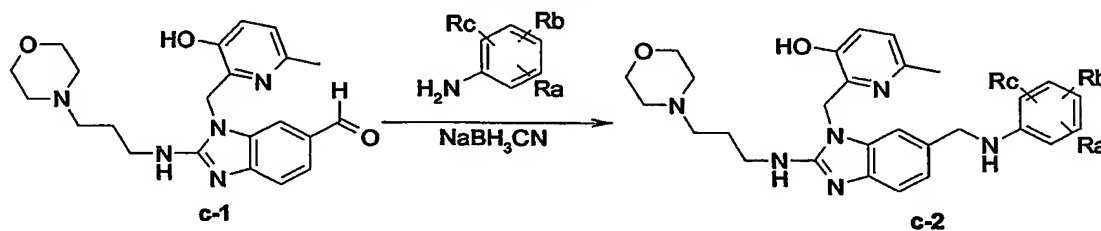
- A mixture of **b-2** (0.069 mol) and N-propylamino-morpholine (0.207 mol) was stirred at 125°C for 4 hours, and then taken up in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$. The organic layer was washed with a 10% solution of K_2CO_3 in water, dried (over MgSO_4), filtered and the
- 15 solvent was evaporated till dryness. The residue (37g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 90/10/0.5; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 16.5g of intermediate **b-3** (82%).

- 20 A mixture of **b-3** (0.0396 mol), **b-4** (0.0475 mol) and K_2CO_3 (0.1188 mol) in dimethylformamide (110ml) was stirred at room temperature for 12 hours. The reaction was poured out into ice/water. The aqueous layer was saturated with K_2CO_3 (powder) and extracted with a solution of $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (95/5). The residue was purified by chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 90/10/1; 20-45 μm).
- 25 The pure fractions were collected and the solvent was evaporated, yielding 5.4g of

intermediate **b-5** (33%, melting point: 192°C) and 5g of intermediate **b-6** (31%, melting point: 134°C).

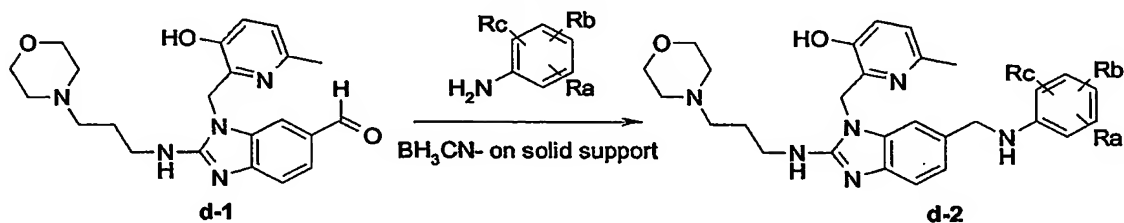
- 5 SOCl_2 (0.81ml) was added drop wise to a mixture of **b-5** (0.0006 mol) in CH_2Cl_2 (10ml) at 5°C. The mixture was stirred at 5°C for 2 hours, then brought to room temperature and stirred for 12 hours. The solvent was evaporated till dryness, yielding 0.42g of intermediate **b-7** (100%).

Scheme C



- 10 $\text{CH}_3\text{CO}_2\text{H}$ (0.2ml) was added at room temperature to a mixture of **c-1** (0.0004 mol), 3,5-dimethyl-aniline (0.0005 mol) and NaBH_3CN (0.0005 mol) in CH_3CN (25ml). The mixture was stirred at room temperature for 30 minutes. $\text{CH}_3\text{CO}_2\text{H}$ (0.2ml) was added. The mixture was stirred at room temperature for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2 . The organic layer was washed with a
- 15 10% solution of K_2CO_3 in water, dried (over MgSO_4), filtered and the solvent was evaporated till dryness. The residue (0.24g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 90/10/0.2; 10 μm). The pure fractions were collected and the solvent was evaporated. The residue (0.15g, 60%) was
- 20 crystallized from 2-propanone/ CH_3CN /diisopropylether. The precipitate was filtered off and dried, yielding 0.121g of 2-[6-[(3,5-dimethyl-phenylamino)-methyl]-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (48%, melting point: 199°C).

Scheme D

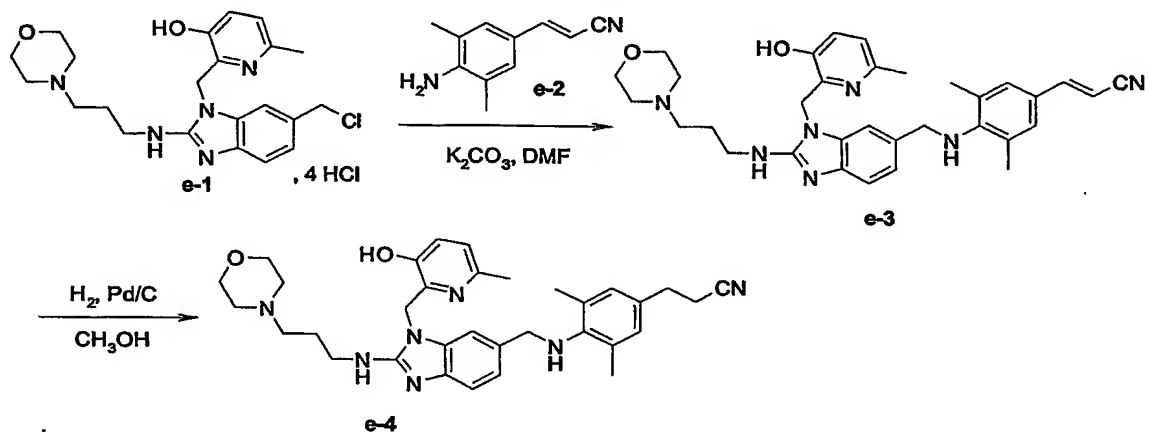


- 25 $\text{CH}_3\text{CO}_2\text{H}$ (0.15ml) was added at room temperature to a mixture of **d-1** (0.00037 mol), 2-(2-amino-4-methyl-phenyl)-ethanol (0.00044 mol) and BH_3CN on solid support (0.00055 mol) in CH_3OH (10ml). The mixture was stirred at room temperature for 12 hours. The solid support was filtered off, rinsed with CH_3OH and the filtrate was concentrated. The residue was taken up in a 10% solution of K_2CO_3 in water and

extracted with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (95/5). The organic layer was separated, dried (over MgSO_4), filtered and the solvent was evaporated till dryness. The residue (0.22g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 93/7/0.5; $10\mu\text{m}$). The pure fractions were collected and the solvent was evaporated.

- 5 The residue (0.13g, 65%) was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.114g of 2-[6-{[2-(2-hydroxy-ethyl)-5-methyl-phenylamino]-methyl}-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (57%, melting point: 199°C).

Scheme E



10

- A mixture of **e-1** (0.000347 mol), **e-2** (0.00041 mol) and K_2CO_3 (0.00173 mol) in dimethylformamide (10 ml) was stirred at 80°C for 3 hours. The reaction was cooled down to room temperature and was poured out into a 10% solution of K_2CO_3 in water. The solution was saturated with K_2CO_3 (powder) and extracted with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (95/5). The organic layer was separated, dried (over MgSO_4), filtered and the solvent was evaporated till dryness. The residue (0.15g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 95/5/0.5; $10\mu\text{m}$). The pure fractions were collected and the solvent was evaporated, yielding 0.03g of intermediate **e-3** (15%, mixture E/Z (89/11)).

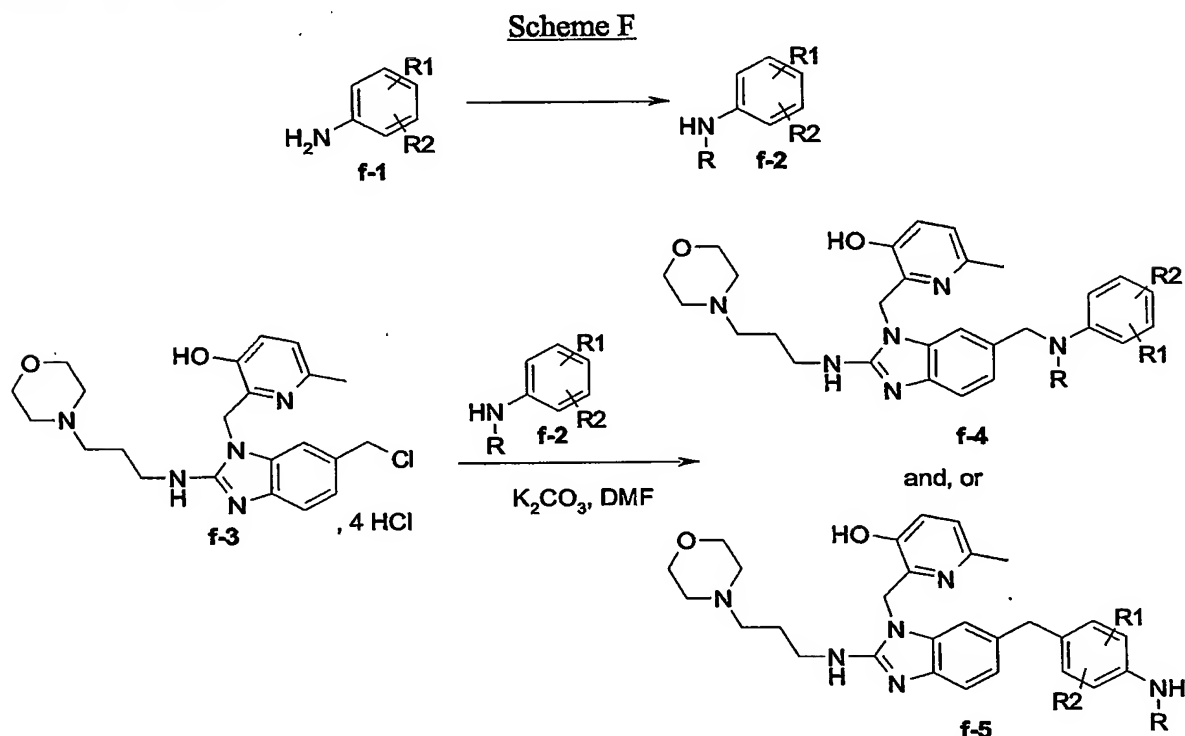
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- A mixture of **e-3** (0.000106 mol) and Pd/C 10% (0.020g) in CH_3OH (15 ml) and tetrahydrofuran (15 ml) was hydrogenated at room temperature for 6 hours under a 3 bar pressure. The reaction was filtered over celite. Celite was rinsed and the filtrate was evaporated till dryness. The residue (0.06g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 93/7/0.5; $10\mu\text{m}$). The pure fractions were collected and the solvent was evaporated. The residue (0.028g) was crystallized from 2-propanone/diisopropylether, yielding 0.021g of 3-(4-{[3-(3-hydroxy-6-methyl-

25

pyridin-2-ylmethyl)-2-(3-morpholin-4-yl-propylamino)-3H-benzoimidazol-5-yl-methyl]-amino}-3,5-dimethyl-phenyl)-propionitrile (35%, melting point: 114°C).

- 5 The isomers substituted in 5 position on the benzimidazole moiety have been synthesized analogous to the procedures described in schemes C and D, starting from intermediate a-10.



- 10 a. A mixture of 3-bromo-aniline (0.037 mol), 2-bromo-ethanol (0.074 mol) and triethylamine (0.0555 mol) in toluene (35ml) was stirred under reflux for 12 hours. The reaction was cooled down to room temperature and the precipitate was filtered off. The solvent of the filtrate was evaporated till dryness. The residue (22g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 98/2/0.1; 20-45μm). The pure fractions were collected and the solvent was evaporated, yielding 4.8g of 2-(3-bromo-phenylamino)-ethanol (60%). 5-(3,5-dimethyl-phenylamino)-pentanoic acid ethyl ester and 3-(3-bromo-phenylamino)-propionic acid ethyl ester and 4-*m*-tolylamino-butane-1-sulfonic acid amide and phosphoric acid 2-(3,5-dimethyl-phenylamino)-ethyl ester diethyl ester and [2-(3,5-dimethyl-phenylamino)-ethyl]-phosphonic acid diethyl ester and 4-*m*-tolylamino-butane-1-sulfonic acid methylamide were prepared analogously.
- 15
- 20 b. A mixture of 3,5-dimethyl-aniline (0.04 mol), 2-bromo-ethanol (0.033 mol) and K₂CO₃ (0.033 mol) in CH₃CN (50 ml) was stirred at 80°C for 12 hours. The reaction was cooled down to room temperature and the solvent was evaporated.

The residue was taken up in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (95/5) and washed with a saturated solution of K_2CO_3 in water. The organic layer was separated, dried (over MgSO_4), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 98/2/0.1; 20-45 μm). The pure fractions were collected and the solvent was evaporated, yielding 1.9g of 2-(3,5-dimethyl-phenylamino)-ethanol (29%). 3-(3,5-dimethyl-phenylamino)-propionic acid ethyl ester and 4-(3,5-dimethyl-phenylamino)-butyric acid ethyl ester and (3,5-dimethyl-phenyl)-(2-morpholin-4-yl-ethyl)-amine and [2-(3,5-dimethyl-phenylamino)-ethyl]-carbamic acid tert-butyl ester were prepared analogously.

- c. 3-(3,5-dimethyl-phenylamino)-propionic acid ethyl ester (0.0026 mol) in a 7N solution of NH_3 in CH_3OH was stirred at 80°C in a sealed vessel. The reaction was cooled down to room temperature and the solvent was evaporated till dryness, yielding 0.5g of 3-(3,5-dimethyl-phenylamino)-propionamide (100%). 4-(3,5-dimethyl-phenylamino)-butyramide and 4-*m*-tolylamino-butyramide and 3-*m*-tolylamino-propionamide and 3-(3-bromo-phenylamino)-propionamide were prepared analogously.
- d. 3-(3,5-dimethyl-phenylamino)-propionic acid ethyl ester (0.00226 mol) in tetrahydrofuran (5 ml) was added drop wise to a slurry of LiAlH_4 (0.0034 mol) in tetrahydrofuran (10 ml) at 5°C under N_2 flow. The mixture was stirred at 5°C for 1 hour. A minimum of water and $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (95/5) were added. The solution was dried (over MgSO_4), filtered and the solvent was evaporated till dryness, yielding 0.35g of 3-(3,5-dimethyl-phenylamino)-propan-1-ol (86%). 5-(3,5-dimethyl-phenylamino)-pentan-1-ol was prepared analogously.

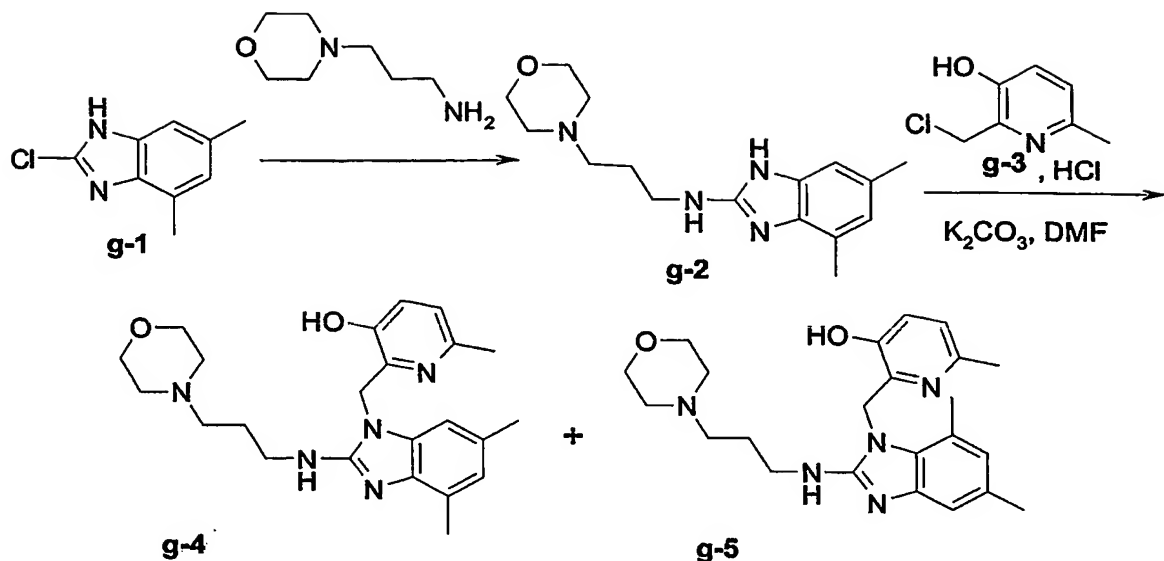
A mixture of f-3 (0.000695 mol), 2-(3,5-dimethyl-phenylamino)-ethanol (0.0009 mol) and K_2CO_3 (0.0035 mol) in dimethylformamide (40ml) was stirred at 80°C for 4 hours. H_2O was added. The solution was saturated with K_2CO_3 (powder) and extracted with $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ (95/5). The organic layer was separated, dried (over MgSO_4), filtered and the solvent was evaporated. The residue (0.5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 93/7/0.5; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 0.120g of fraction 1 (31%) and 0.045g of fraction 2 (12%). Fraction 1 was crystallized from $\text{CH}_3\text{CN}/$ diisopropylether. The precipitate was filtered, rinsed with diisopropylether and dried, yielding 0.1g of 2-[6-[[3,5-dimethyl-phenyl)-(2-hydroxy-ethyl)-amino]-methyl]-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (example of compound f-4; 26%, melting point: 180°C). Fraction 2 was crystallized from 2-propanone/diisopropylether. The precipitate was filtered, rinsed with

diisopropylether and dried, yielding 0.016g of 2-[6-[4-(2-hydroxy-ethylamino)-2,6-dimethyl-benzyl]-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (4%, melting point: 162°C).

- 5 A mixture of 4-{{(3,5-dimethyl-phenyl)-[3-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-2-(3-morpholin-4-yl-propylamino)-3H-benzoimidazol-5-ylmethyl]-amino}-butyric acid ethyl ester, prepared as described for compounds f-4, (0.000175 mol) and LiOH/H₂O (0.00035) in tetrahydrofuran (8 ml) and H₂O (8 ml) was stirred at room temperature for 12 hours. The tetrahydrofuran was evaporated and a 1 N solution of NaOH in water
10 was added. The solution was extracted with CH₂Cl₂/CH₃OH (95/5). The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated. The residue was taken up in H₂O. The precipitate was filtered off and dried, yielding 0.059g of 4-{{(3,5-dimethyl-phenyl)-[3-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-2-(3-morpholin-4-yl-propylamino)-3H-benzoimidazol-5-ylmethyl]-amino}-butyric acid
15 (56%, melting point: 121°C).

- A mixture of (2-{{(3,5-dimethyl-phenyl)-[3-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-2-(3-morpholin-4-yl-propylamino)-3H-benzoimidazol-5-ylmethyl]-amino}-ethyl)-carbamic acid tert-butyl ester, prepared as described for compounds f-4, (0.00012) in a
20 3N solution of HCl in water (10 ml) and tetrahydrofuran (10 ml) was stirred at room temperature for 12 hours. The precipitate was filtered off and taken up in a 10% solution of K₂CO₃ in water. The solution was saturated with K₂CO₃ (powder) and extracted with CH₂Cl₂/CH₃OH (95/5). The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue (0.07g) was
25 purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 92/8/1; 10µm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN/CH₃OH/ diisopropylether, yielding 0.03g of 2-[6-{{[(2-amino-ethyl)-(3,5-dimethyl-phenyl)-amino]-methyl}-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (44%, melting point:
30 196°C).

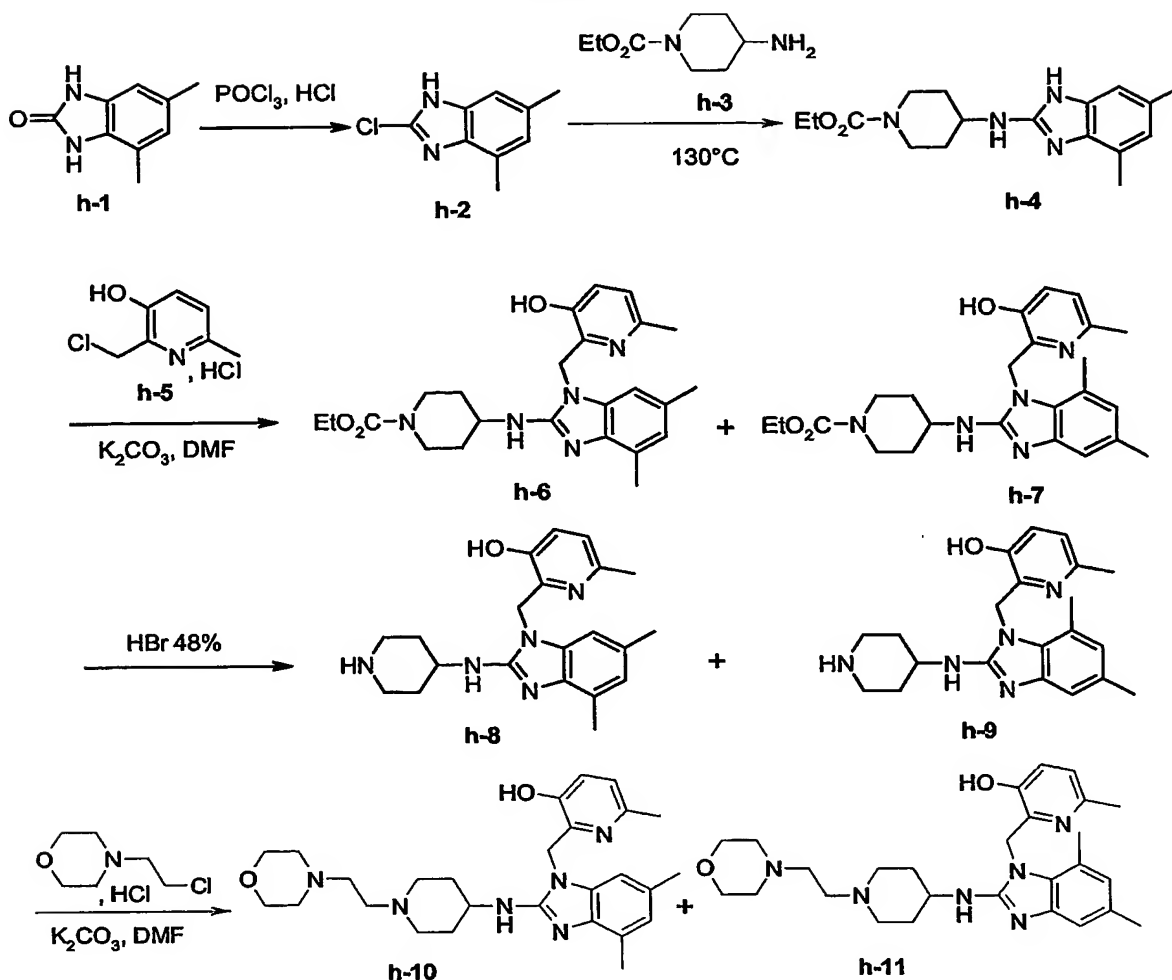
Scheme G



A mixture of **g-1** (0.0011 mol) and N-(propylamino)-morpholine (0.0044 mol) was stirred at 130°C for 4 hours, then brought to room temperature, taken up in H₂O and extracted with CH₂Cl₂. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated. The residue (0.328g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/triethylamine 99/1/0.1 to 90/10/1; 10μm). The pure fractions were collected and the solvent was evaporated, yielding 0.216g of intermediate **g-2** (68%).

A mixture of **g-2** (0.0007 mol), **g-3** (0.0008 mol) and K₂CO₃ (0.003 mol) in dimethylformamide (6ml) was stirred at 70°C for 12 hours, then brought to room temperature, taken up in H₂O and extracted with CH₂Cl₂. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated. The residue (0.5g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 93/7/0.5 then toluene/iPrOH/NH₄OH 80/20/1; 10μm). Two fractions were collected and the solvent was evaporated, yielding 0.13g of fraction 1 and 0.036g of fraction 2. Fraction 1 was taken up in diisopropylether. The precipitate was filtered off and dried, yielding 0.1g of 2-[4,6-dimethyl-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (33%, melting point: 228°C). Fraction 2 was taken up in diisopropylether. The precipitate was filtered off and dried, yielding 0.03g of 2-[5,7-dimethyl-2-(3-morpholin-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (10%, melting point: 234°C).

Scheme H



The mixture of **h-1** (0.06 mol) and POCl₃ (100 ml) was heated at 100°C and HCl 12N (2.5 ml) was added drop wise very carefully. The reaction was then stirred during 12 hours at 120°C and allowed to cool down to room temperature. The solvent was evaporated under reduced pressure and a 10% solution of potassium carbonate in water was added to the residue. The resulting precipitate was filtered off, rinsed with water and dried, yielding 10 g of **h-2** (93%, melting point = 152°C).

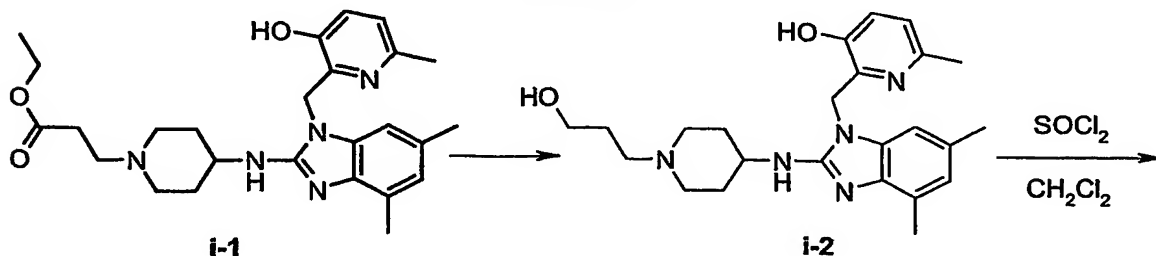
h-2 (0.022 mol) and **h-3** (0.088 mol) were stirred at 130°C during 12 hours. The reaction was then allowed to cool down to room temperature, the residue was taken up in acetone and the precipitate was filtered off. The acetone solution was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/MeOH/NH₄OH 95/5/0.1). The pure fractions were collected and the solvent was evaporated, yielding 5 g of **h-4** (72%).

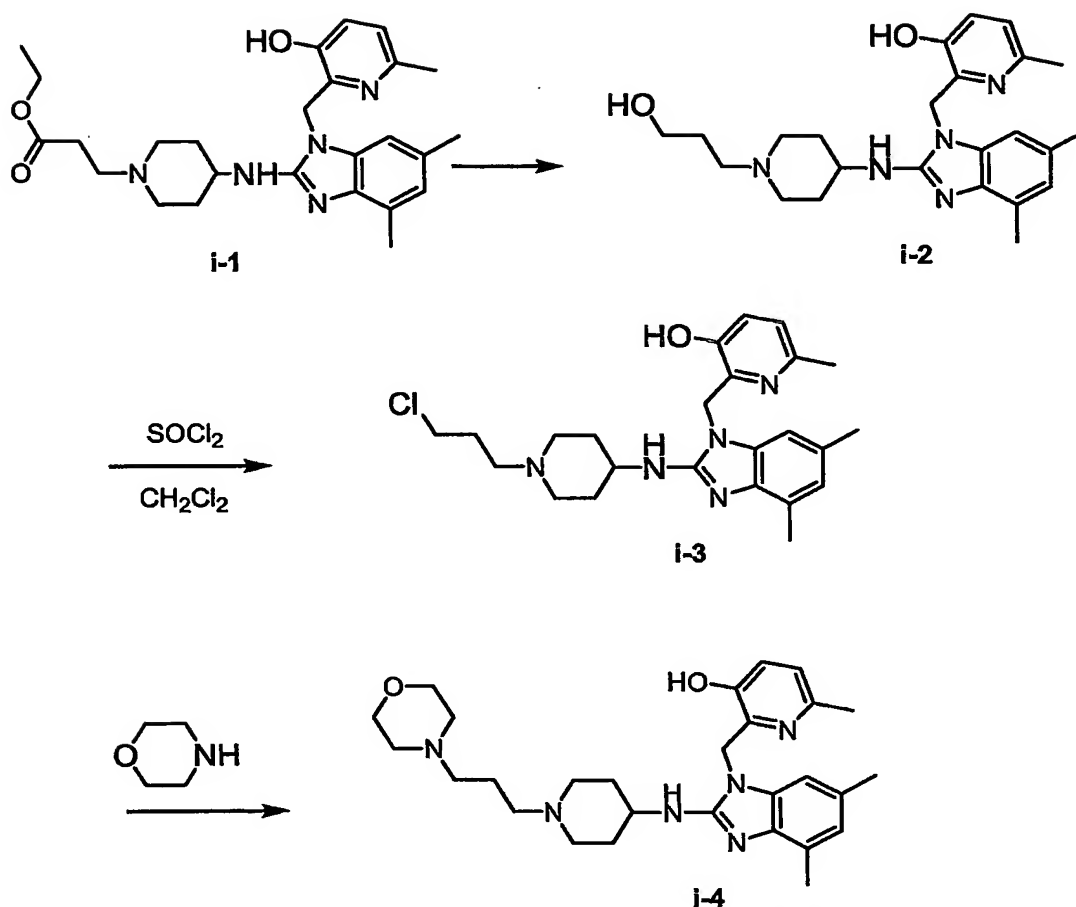
A mixture of **h-4** (0.0158 mol), **h-5** (0.019 mol) and potassium carbonate (0.0553 mol) in dimethylformamide (100ml) was stirred at 70°C for 24 hours. The solvent was evaporated till dryness. The residue was taken up in CH₂Cl₂/CH₃OH (90/10). The organic layer was washed with a 10% solution of K₂CO₃ in water, dried (over MgSO₄),
 5 filtered and the solvent was evaporated under reduced pressure. The residue was taken up in 2-propanone. The precipitate was filtered off, washed with H₂O and dried, yielding 5g of **h-6** and **h-7** (50/50 mixture, 73%).

A mixture of **h-6** and **h-7** (0.0103 mol) in a 48% solution of HBr in water (50ml) was stirred at 60°C during 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH₂Cl₂/CH₃OH (90/10). 10% solution of K₂CO₃ in water was added. The aqueous layer was saturated with K₂CO₃ (powder). The organic layer was separated, dried (over MgSO₄), filtered, and the solvent was evaporated till dryness, yielding 3.7g of **h-8** and **h-9** (100%). This product was used directly in the next
 15 reaction step.

A mixture of **h-8** (0.0006 mol), **h-9** (0.0006 mol), N-(2-chloro-ethyl)-morpholine, HCl (0.0016 mol) and K₂CO₃ (0.0048 mol) in dimethylformamide (30ml) was stirred at room temperature for 48 hours. The solvent was evaporated till dryness. The residue was taken up in CH₂Cl₂. The mixture was filtered. The filtrate was evaporated till dryness. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 90/10/0.5; 10µm). Two fractions were collected and the solvent was evaporated, yielding 0.023g of fraction 1 (4%) and 0.12g of fraction 2 (18%). Fraction 1 was crystallized from CH₃OH/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.02g of 2-[5,7-dimethyl-2-(2-morpholin-4-ylethyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-6-methylpyridin-3-ol (3%, melting point: 226°C). Fraction 2 was crystallized from CH₃OH/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.1g of 2-[4,6-dimethyl-2-(2-morpholin-4-ylethyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-6-methylpyridin-3-ol (15%, melting point: 237°C).
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Scheme I



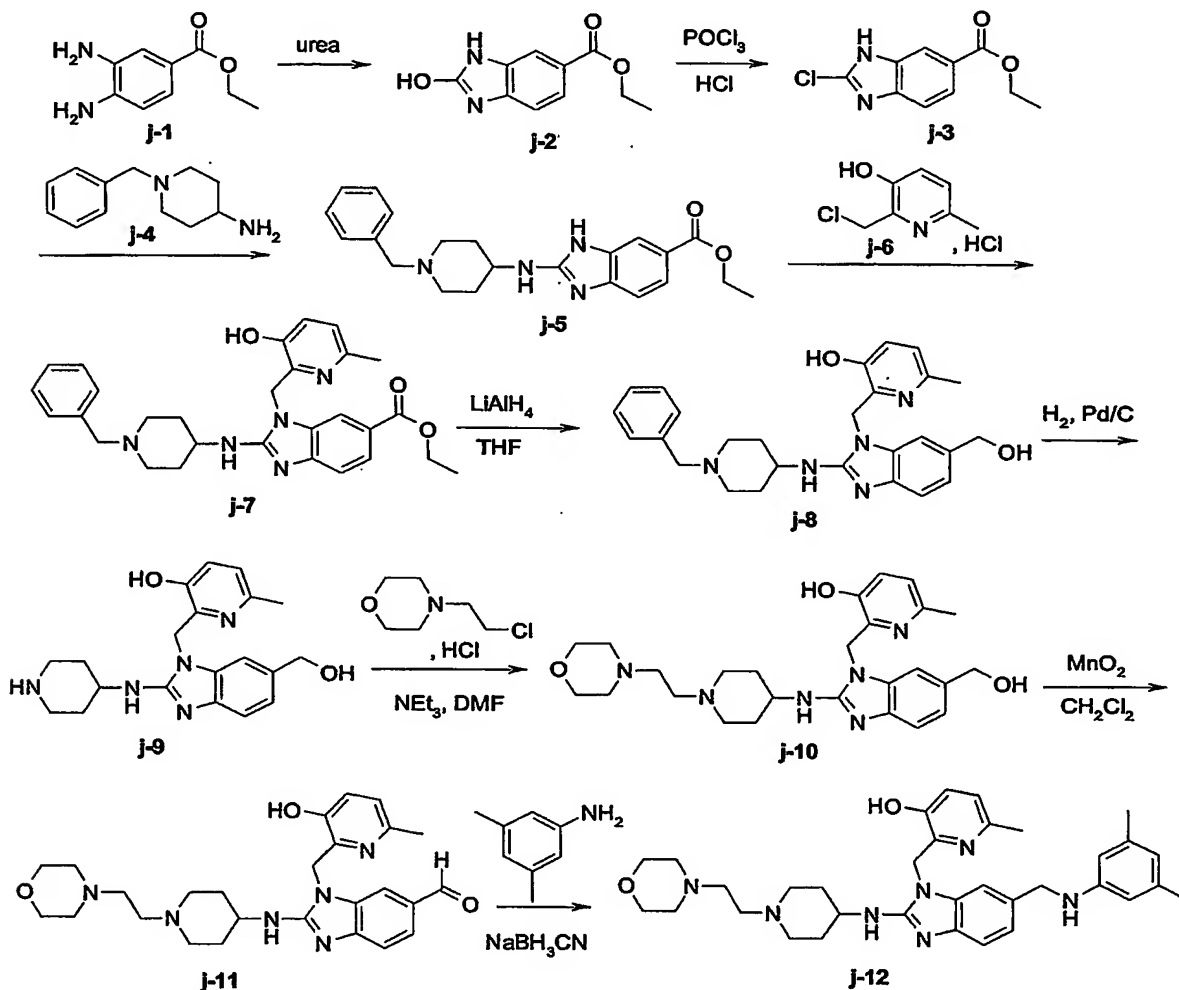


LiAlH₄ (0.0002 mol) was added at 5°C to a mixture of 3-{4-[1-(3-hydroxy-6-methyl-pyridin-2-ylmethyl)-4,6-dimethyl-1H-benzoimidazol-2-ylamino]-piperidin-1-yl}-propionic acid ethyl ester (i-1; 0.00009 mol; melting point: 172°C; in tetrahydrofuran (10ml) under N₂ flow. The mixture was stirred at 5°C for 1 hour, then at room temperature for 3 hours. A minimum of H₂O and ethylacetate were added. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was crystallized from 2-propanone/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.026g of 2-{2-[1-(3-hydroxy-propyl)-piperidin-4-ylamino]-4,6-dimethyl-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (i-2; 68%, melting point: 209°C).

A mixture of i-2 (0.0001 mol) and CH₂Cl₂ (15ml) was cooled in a bath of ice. SOCl₂ (0.0005 mol) was added drop wise. The mixture was stirred at 5°C for 1 hour, then at room temperature for 12 hours. SOCl₂ (0.0005 mol) was added. The mixture was stirred at room temperature for 4 hours. The solvent was evaporated till dryness, yielding 0.06g of intermediate i-3 (100%). This product was used directly in the next reaction step.

A mixture of **i-3** (0.0001 mol), morpholine (0.0003 mol) and K_2CO_3 (0.0011 mol) in CH_3CN (15ml) was stirred at $70^\circ C$ for 6 hours. The solvent was evaporated till dryness. The residue was taken up in CH_2Cl_2/H_2O . The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (0.06g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 88/11/1; $5\mu m$). The pure fractions were collected and the solvent was evaporated, yielding 0.016g of 2-[4,6-dimethyl-2-(2-morpholin-4-ylpropyl-piperidin-4-ylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (18%, melting point: $223^\circ C$).

Scheme J



10

A mixture of **j-1** (0.166 mol) and urea (0.199 mol) in xylene (300 ml) was stirred under reflux for 12 hours. The reaction was cooled down to room temperature. The precipitate was filtered off, rinsed with xylene and diisopropylether, and then dried, yielding 32g of intermediate **j-2** (93%, melting point: $> 260^\circ C$).

15

A mixture of **j-2** (0.073 mol) in POCl₃ (150 ml) was stirred at 100°C. HCl conc. (around 1.5 ml) was added drop wise very carefully until the dissolution of **j-2**. The mixture was stirred at 120°C for 6 hours. The solvent was evaporated till dryness. The residue was taken-up in H₂O/ice, basified with K₂CO₃ (powder) and extracted with ethylacetate + 10% methanol. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness, yielding 13.5 g of intermediate **j-3** (83%, melting point: 178°C).

A mixture of **j-3** (0.051 mmol) and **j-4** (0.056 mol) was stirred at 160°C for 2 hours. The residue was taken-up in CH₂Cl₂/H₂O and basified with a 10% solution of K₂CO₃ in water. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/methanol/NH₄OH 95/5/0.5). The pure fractions were collected and the solvent was evaporated, yielding 15.3 g of intermediate **j-5** (79%).

A mixture of **j-5** (0.0396 mol), **j-6** (0.059 mol) and K₂CO₃ (0.1584 mol) in CH₃CN (180ml) was stirred and refluxed for 12 hours. The solvent was evaporated till dryness. The residue was taken up in CH₂Cl₂. The organic layer was washed with H₂O, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue (20g) was purified by column chromatography over silica gel (eluent: Toluene/2-propanol/NH₄OH 85/15/1; 20-45µm). Two fractions were collected and the solvent was evaporated, yielding 5.3g of fraction 1 (27%) and 6.3g of fraction 2 (32%). Fraction 1 was crystallized twice in 2-propanone/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 4.9g of intermediate **j-7** (25%, melting point: 179°C).

LiAlH₄ (0.009 mol) was added portion wise to a mixture of **j-7** (0.003 mol) in tetrahydrofuran (60 ml) at 5°C under N₂ flow. The reaction was stirred at 5°C for 1 hour and then at room temperature for 12 hours. Ethylacetate and H₂O were added carefully and the aqueous layer was saturated with K₂CO₃ (powder). The organic layer was separated, dried (over MgSO₄) and then filtered over celite. The filtrate was evaporated till dryness, yielding 1.3 g of intermediate **j-8** (97%). The crude product was used directly in the next reaction step.

A mixture of **j-8** (0.0028 mol) and Pd/C 10% (2.5g) in CH₃OH (40ml) was hydrogenated at 40°C for 12 hours under an 8 bar pressure, then filtered over celite. Celite was washed with a solution of CH₃OH/tetrahydrofuran (50/50). The filtrate was evaporated till dryness, yielding 1.8g of intermediate **j-9** (95%, melting point: 260°C).

A mixture of **j-9** (0.0027 mol), N-(2-chloro-ethyl)-morpholine, HCl (0.0032 mol) and triethylamine (0.0067 mol) in dimethylformamide (40ml) was stirred at 50°C for 48 hours, poured out into ice water and extracted 3 times with CH₂Cl₂. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness.

5 The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH; 85/14/1; 35-70μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.8g of intermediate **j-10** (61%, melting point: 147°C).

10

A mixture of **j-10** (0.0014 mol) and MnO₂ (1.6g) in CH₂Cl₂ (50ml) was stirred at room temperature for 12 hours, and then filtered over celite. The solvent of the filtrate was evaporated till dryness. The residue was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.47g of intermediate **j-11** (67%, melting point: 136°C).

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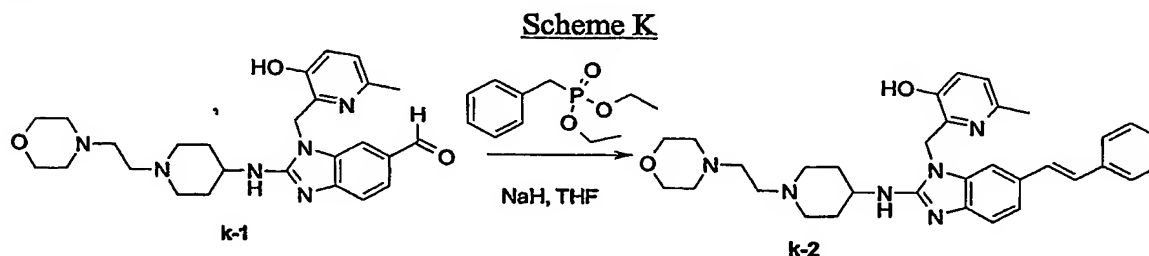
CH₃CO₂H (0.3ml) was added at room temperature to a mixture of **j-11** (0.0005 mol), 3,5-dimethyl-aniline (0.0006 mol) and NaBH₃CN (0.0006 mol) in CH₃CN (30ml). The mixture was stirred at room temperature for 30 minutes. CH₃CO₂H (0.3ml) was added.

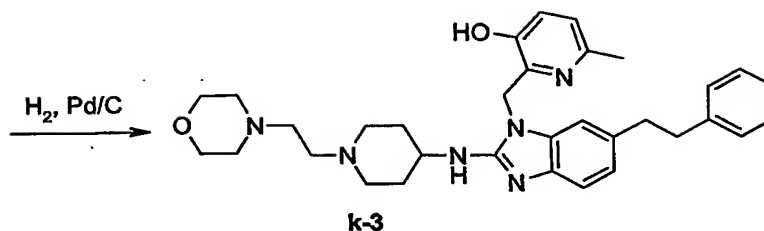
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The mixture was stirred at room temperature for 6 hours. The solvent was evaporated till dryness. The residue was taken up in CH₂Cl₂. The organic layer was washed with a 10% solution of K₂CO₃ in water, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue (0.26g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 90/10/1; 5μm). The pure fractions were collected and the solvent was evaporated. The residue (0.12g, 36%) was crystallized from CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.07g of 2-{6-[(3,5-dimethyl-phenylamino)-methyl]-2-[2-(2-morpholin-4-yl-ethyl)-piperidin-4-ylamino]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (21%, melting point: 150°C).

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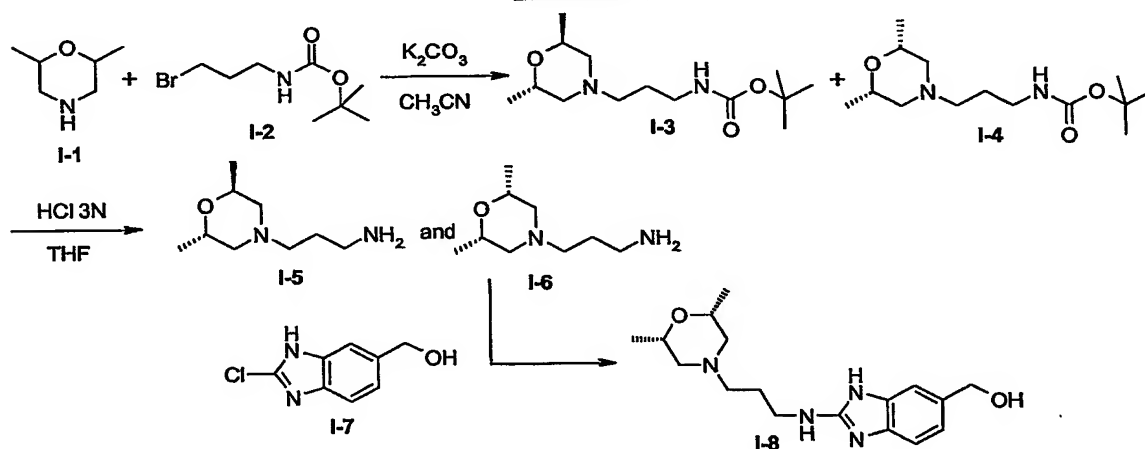


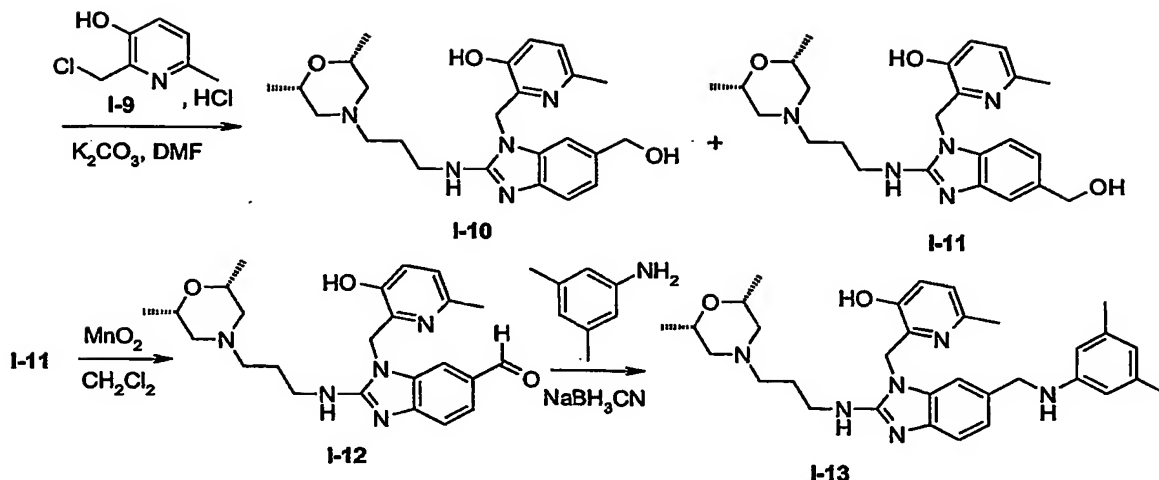


Benzyl-diethylphosphonate (0.0019 mol) was added to a mixture of NaH (0.0037 mol) in tetrahydrofuran (15ml) at 5°C under N₂ flow. The mixture was stirred at 5°C for 30 minutes. A solution of k-1 (0.0006 mol) in tetrahydrofuran (10ml) was added drop wise. The mixture was stirred at 5°C for 1 hour, then at room temperature for 12 hours. H₂O was added. The mixture was extracted with ethylacetate. The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was crystallized from CH₃OH. The precipitate was filtered off and dried, yielding 0.13g of 6-methyl-2-{2-[2-(2-morpholin-4-yl-ethyl)-piperidin-4-ylamino]-6-styryl-benzoimidazol-1-ylmethyl}-pyridin-3-ol (k-2; 37%, melting point: 224°C).

A mixture of k-2 (0.0002 mol) and Pd/C 10% (0.035g) in CH₃OH (5ml) and tetrahydrofuran (5ml) was hydrogenated at room temperature for 6 hours under a 8 bar pressure, and then filtered over celite. Celite was washed with H₂O. The filtrate was evaporated till dryness. The residue was taken up in 2-propanone. The precipitate was filtered, washed with H₂O and dried, yielding 0.08g of 6-methyl-2-{2-[2-(2-morpholin-4-yl-ethyl)-piperidin-4-ylamino]-6-phenethyl-benzoimidazol-1-ylmethyl}-pyridin-3-ol (72%, melting point: 159°C).

Scheme L





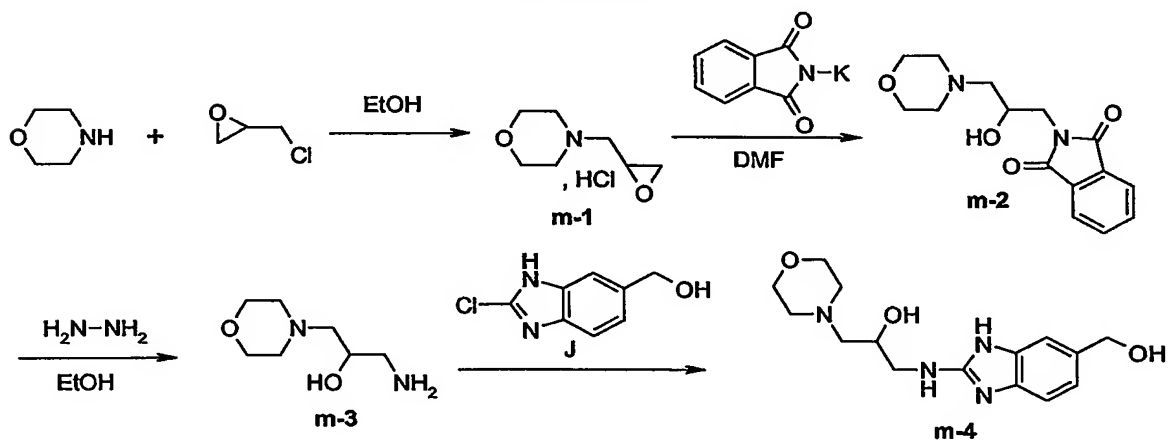
- A mixture of I-1 (mixture cis + trans) (0.0379 mol), I-2 (0.0416 mol) and K_2CO_3 (0.1136 mol) was stirred at 80°C for 12 hours. H_2O was added. The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue (10g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 97/3/0.1; 35-70 μm). Two fractions were collected and the solvent was evaporated, yielding 3g of intermediate I-3 (trans) (29%) and 7.3g of intermediate I-4 (cis) (71%).
- 10 A mixture of I-4 (0.0279 mol) in a 3N solution of HCl in water (50ml) and tetrahydrofuran (50ml) was stirred at room temperature for 12 hours. K_2CO_3 (powder) was added. CH_2Cl_2 was added. The aqueous layer was saturated with K_2CO_3 (powder). The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated, yielding 4.39g of intermediate I-6 (93%). Analogously, I-5 was prepared.
- 15 A mixture of I-7 (0.0085 mol) and I-6 (0.0255 mol) was stirred at 120°C for 4 hours. A 10% solution of K_2CO_3 in water was added. The aqueous layer was saturated with K_2CO_3 (powder). The mixture was extracted with CH_2Cl_2 . The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated. The residue (4.1g) was purified by column chromatography over silica gel (eluent: $CH_2Cl_2/CH_3OH/NH_4OH$ 90/10/1; 15-40 μm). The pure fractions were collected and the solvent was evaporated, yielding 1.6g of intermediate I-8 (59%).
- 20 A mixture of I-8 (0.0048 mol), C (0.0058 mol) and K_2CO_3 (0.0145 mol) in dimethylformamide (30ml) was stirred at room temperature for 24 hours, poured out into H_2O , saturated with K_2CO_3 (powder) and extracted with CH_2Cl_2/CH_3OH . The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness. The residue (3.3g) was purified by column chromatography over silica gel (eluent:

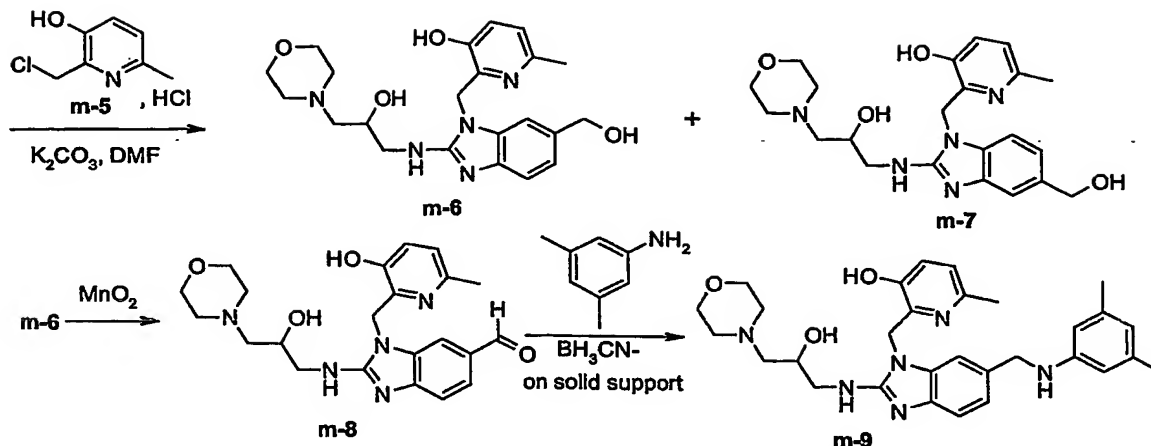
CH₂Cl₂/CH₃OH/NH₄OH 90/10/0.5; 15-40μm). Two fractions were collected and the solvent was evaporated, yielding 0.55g of intermediate **l-10** (26%) and 0.36g of intermediate **l-11** (17%). A small fraction of intermediate **l-10** was crystallized from 2-propanone/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.04g (melting point: 199°C). A small fraction of intermediate **l-11** was crystallized from 2-propanone/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.04g (melting point: 227°C).

A mixture of **l-11** (0.0011 mol) and MnO₂ (1g) in CH₂Cl₂ (50ml) and CH₃OH (3ml) was stirred at room temperature for 12 hours, and then filtered over celite. Celite was washed with H₂O. The filtrate was evaporated till dryness, yielding 0.5g of intermediate **l-12** (100%). The crude product was used directly in the next reaction step.

CH₃CO₂H (0.25ml) was added to a mixture of **l-12** (0.0005 mol), 3,5-dimethyl-aniline (0.0006 mol) and NaBH₃CN (0.0006 mol) in CH₂Cl₂ (30ml). The mixture was stirred at room temperature for 12 hours. A 10% solution of K₂CO₃ in water was added. The mixture was saturated with K₂CO₃ (powder). The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 35-70μm). The pure fractions were collected and the solvent was evaporated. The residue (0.25g, 80%) was crystallized from 2-propanone/CH₃CN/diisopropylether. The precipitate was filtered off and dried, yielding 0.183g of 2-{2-[3-(2,6-dimethyl-morpholin-4-yl)-propylamino]-6-[(3,5-dimethyl-phenylamino)-methyl]-benzoimidazol-1-ylmethyl}-6-methyl-pyridin-3-ol (59%, melting point: 192°C).

Scheme M





A mixture of morpholine (0.0116 mol), epichlorohydrin (0.0116 mol) in ethanol (30 ml) was stirred at room temperature for 24 hours. The solvent was evaporated till dryness, yielding 2.08g of intermediate **m-1** (100%). The crude product was used directly in the next reaction step.

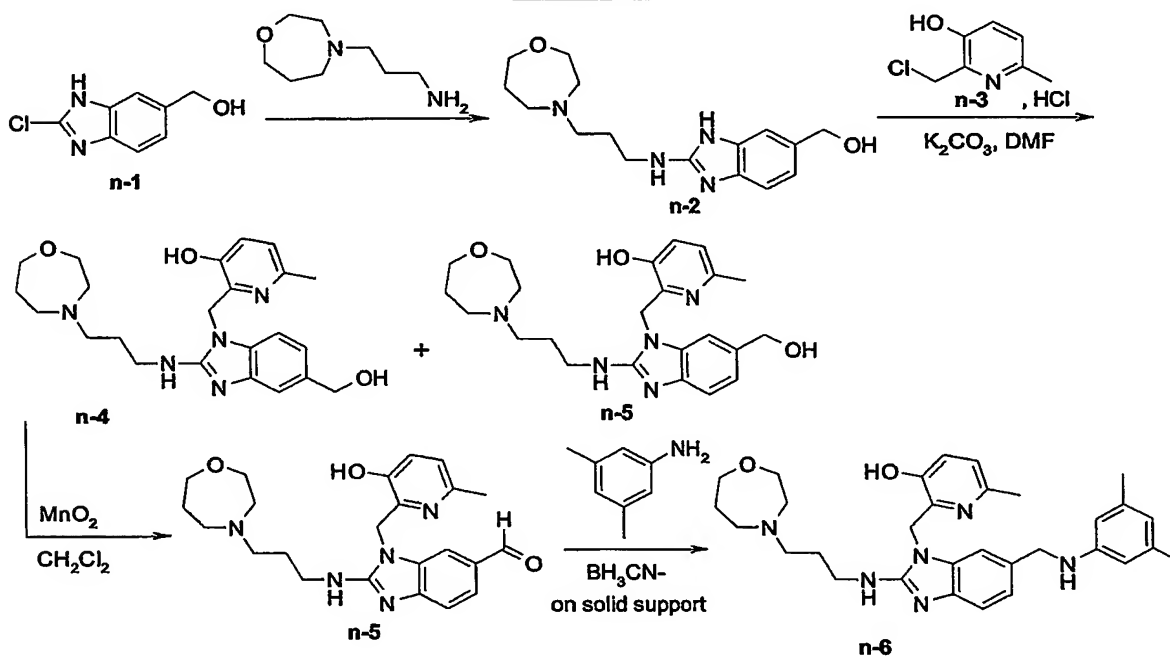
A mixture of **m-1** (0.0116 mol), potassium phthalimide (0.01276 mol) in dimethylformamide (25 ml) was stirred under reflux for 4 hours. The solvent was evaporated. The residue was taken up in CH_2Cl_2 and washed with H_2O . The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness, yielding 3.4g of intermediate **m-2** (100%). The crude product was used directly in the next reaction step.

A mixture of **m-2** (0.116 mol) and hydrazine (15 ml) in ethanol (350 ml) was stirred at $80^\circ C$ for 1 hour. The reaction was cooled down to room temperature. The precipitate was filtered off and rinsed with ethanol and CH_2Cl_2 . A 10% solution of K_2CO_3 in water was added. The aqueous layer was saturated with K_2CO_3 (powder) and extracted with CH_2Cl_2/CH_3OH (95/5). The organic layer was separated, dried (over $MgSO_4$), filtered and the solvent was evaporated till dryness, yielding 14.8g of intermediate **m-3** (80%). The crude product was used directly in the next reaction step.

Intermediate **m-5** was prepared in an analogous way to the procedure described for intermediate **l-8**. Intermediates **m-7** (2g; 31%, melting point: $184^\circ C$) and **m-8** (2.1g; 33%, melting point: $208^\circ C$) were prepared in an analogous way to the procedure described for preparing **l-10** and **l-11**. These compounds have been synthesized according to the procedure described for intermediates **J1** and **K1** and. Intermediate **m-9** (0.77g; 77%, melting point: $152^\circ C$) was prepared in an analogous way to the procedure described for intermediate **l-12**.

CH₃CO₂H (0.2ml) was added at room temperature to a mixture of **m-9** (0.00047 mol), 3,5-dimethyl-aniline (0.00056 mol) and BH₃CN⁻ on solid support (0.000705 mol) in CH₃OH (10ml). The mixture was stirred at room temperature for 18 hours. The solid support was filtered off, rinsed with CH₃OH and the filtrate was concentrated. The residue was taken up with a 10% solution of K₂CO₃ in water. The aqueous layer was saturated with K₂CO₃ (powder) and extracted with CH₂Cl₂/CH₃OH (95/5). The organic layer was separated, dried (over MgSO₄), filtered and the solvent was evaporated till dryness. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 35-70μm). The pure fractions were collected and the solvent was evaporated. The residue (0.2g) was crystallized from 2-propanone/diisopropylether. The precipitate was filtered off and dried, yielding 0.154g of 2-[6-[(3,5-dimethyl-phenylamino)-methyl]-2-(2-hydroxy-3-morpholin-4-yl-propyl-amino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (**m-10**; 62%, melting point: 198°C).

Scheme N



Intermediate **n-2** was prepared in an analogous way to the procedure described for intermediate **l-8**. Intermediates **n-4** (0.28g; 28%) and **n-5** (0.025g; 26%) were prepared in an analogous way to the procedure described for intermediate **l-10** and **l-11**.

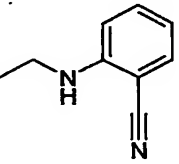
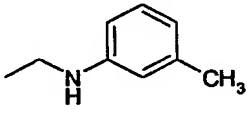
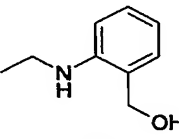
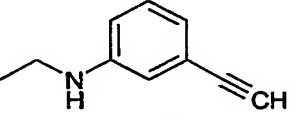
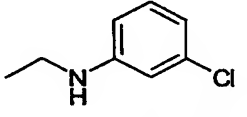
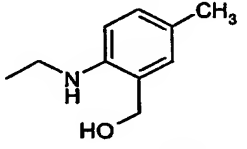
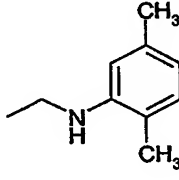
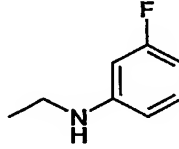
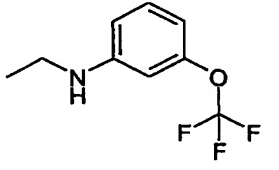
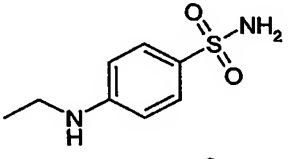
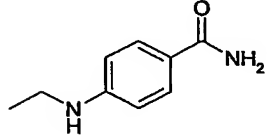
Intermediate **n-6** (0.020g; 80%) was prepared in an analogous way to the procedure described for intermediate **l-12**.

2-[5-[(3,5-Dimethyl-phenylamino)-methyl]-2-(3-[1,4]oxazepan-4-yl-propylamino)-benzoimidazol-1-ylmethyl]-6-methyl-pyridin-3-ol (0.007g; 28%) was prepared in an analogous way to the procedure described for compound m-10.

5 The following tables list compounds that were prepared according to any one of the above examples.

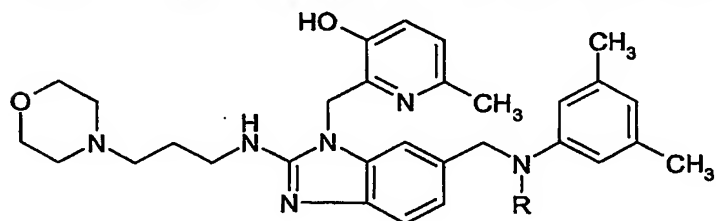
Table 1

Comp. No.	R ^{2a}	R ^{3a}	Activity category	Mass (MH ⁺)	Melting point/salt	Synthesis scheme
1	H		A	545	199°C	D
2	H		A	539-543	206°C	C
3	H		A	531	140°C	D
4	H		A	545	208°C	D
5	H		A	515	199°C	C
6	H		A	565-567	205°C	C

Comp. No.	R ² a	R ³ a	Activity category	Mass (MH ⁺)	Melting point/salt	Synthesis scheme
7	H		A	512	217°C	D
8	H		A	501	195°C	C
9	H		A	517	130°C	D
10	H		A	511	186°C	C
11	H		A	522-524	212°C	C
12	H		A	531	131°C	D
13	H		A	515	209°C	D
14	H		A	505	210°C	C
15	H		A	571	163°C	D
16	H		A	566	> 260°C	D
17	H		A	530	175°C	D

Comp. No.	R ^{2a}	R ^{3a}	Activity category	Mass (MH ⁺)	Melting point/salt	Synthesis scheme
18	H		A	515	210°C	D
19	H		A	531	231°C	D
20	H		A	530	145°C	D
21	H		A	552	150°C	D
22	H		A	568	114°C	E
23		H	A	515	176°C	C
24	H	-CH ₂ -OH	A	412	192°C	A
25	-CH ₂ -OH	H	C	412	134°C	A
	H					D

Table 2 : compounds prepared according to synthesis scheme F



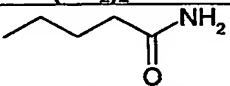
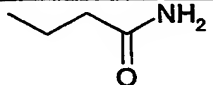
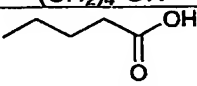
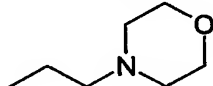
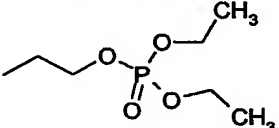
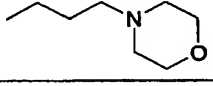
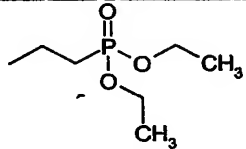
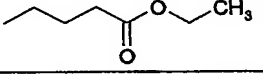
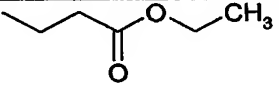
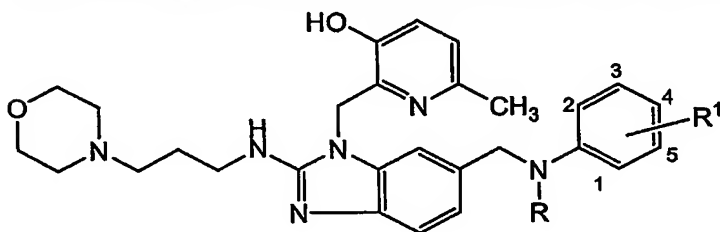
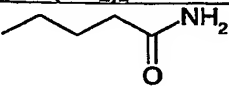
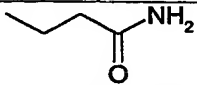
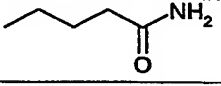
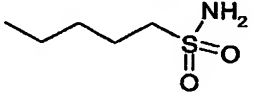
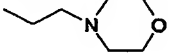
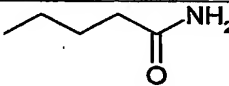
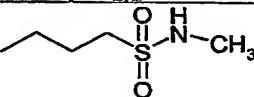
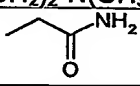
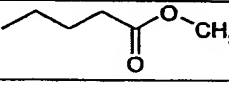
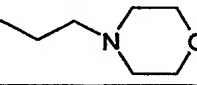
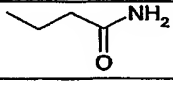
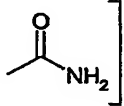
Comp. No.	R	Activity category	Mass (MH ⁺)	Melting point/salt
26	$-(CH_2)_2-OH$	A	559	180°C
27		A	600	170°C
28		A	586	138°C
29	$-(CH_2)_4-OH$	A	587	170°C
30		A	MH ⁺ = 599	121°C
31	$-(CH_2)_3-OH$	A	573	197°C
32	$-(CH_2)_5-OH$	A	601	120°C
33		A	628	169°C
34	$-(CH_2)_2-NH_2$	A	558	196°C
35		A	695	152°C
36		A	642	169°C
37	$-(CH_2)_2-COOH$	A	MH ⁺ = 585	128°C
38		A	679	175°C
39		A	629	130°C
40		A	615	136°C

Table 3 : compounds prepared according to synthesis scheme F



Comp. No.	R	R ¹	Activity category	Mass (MH ⁺)	Melting point/salt
41	$-(CH_2)_2-OH$	3-Br	A	609-611	210°C

Comp. No.	R	R ¹	Activity category	Mass (MH ⁺)	Melting point/salt
42	-(CH ₂) ₂ -OH	5-CH ₃	A	545	205°C
43		3-CH ₃	A	586	139°C
44	-(CH ₂) ₂ -OH	4-CN	A	556	195°C
45		3-CH ₃	A	572	128°C
46		5-Br	A	650-652	180°C
47		5-CH ₃	A	636	140°C
48	-(CH ₂) ₄ -OH	3-CH ₃	A	573	169°C
49	-(CH ₂) ₃ -OH	3-CH ₃	A	559	109°C
50		3-CH ₃	A	614	153°C
51	-(CH ₂) ₃ -OH	5-Br	A	623-625	120°C
52		4-CN	A	597	170°C
53	-(CH ₂) ₂ -OH	H	A	531	190°C
54		5-CH ₃	A	636	125°C
55	-(CH ₂) ₂ -OH	3-[-C≡CH]	A	555	186°C
56	-(CH ₂) ₂ -N(CH ₃) ₂	3-CH ₃	A	572	172°C
57		2-[-(CH ₂) ₂ -OH]	A	588	175°C
58		3-CH ₃	A	601	150°C
59		6-[-(CH ₂) ₂ -OH]	A	644	146°C
60		3-[-(CH ₂) ₂ -OH]	A	602	124°C
61	-(CH ₂) ₂ -OH	4 - 	A	574	130°C
62	phenyl	4-OH	A	579	175°C
63	-(CH ₂) ₂ -OH	6-[-(CH ₂) ₂ -OH]	A	575	165°C
64	H	6-[-CH ₂ -NH ₂]	A	516	116°C
65	phenyl	3-OH	A	579	135°C

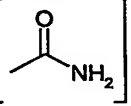
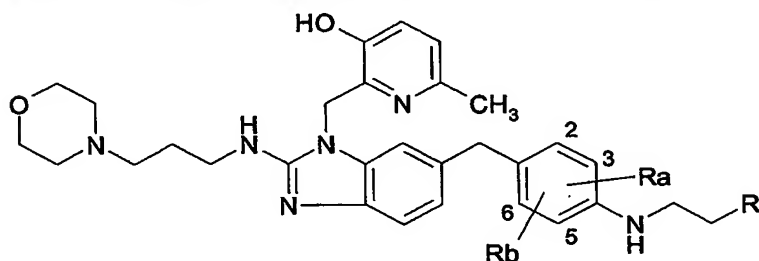
Comp. No.	R	R ¹	Activity category	Mass (MH ⁺)	Melting point/salt
66	-(CH ₂) ₂ -OH	6-CH ₃	A	545	165°C
67	-(CH ₂) ₂ -OH	2- 	A	574	145°C

Table 4 : compounds prepared according to synthesis scheme F



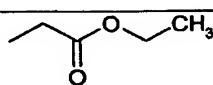
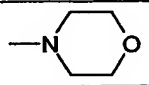
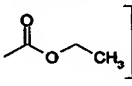
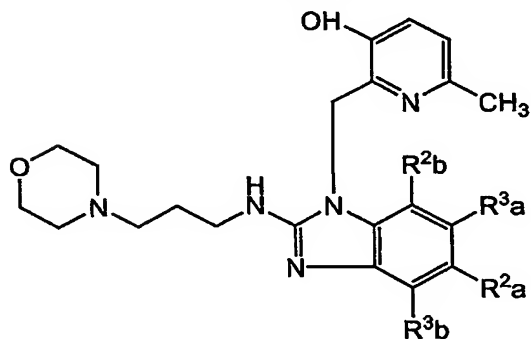
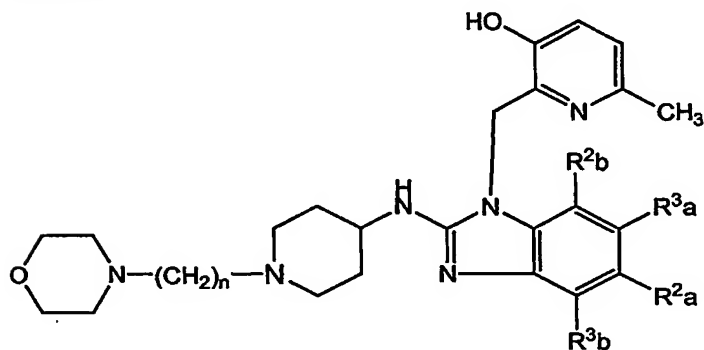
Comp. No.	R	Ra	Rb	Activity category	Mass (MH ⁺)	Melting point/salt
68		2-CH ₃	6-CH ₃	A	629	164°C
69	OH	3-CH ₃	H	A	545	190°C
70	OH	3-OCH ₃	H	A	561	170°C
71	-(CH ₂) ₂ -OH	6-CH ₃	H	A	573	
72	OH	2-CH ₃	6-CH ₃	A	559	162°C
73		2-CH ₃	6-CH ₃	A	628	158°C
74	-N(CH ₃) ₂	2-CH ₃	6-CH ₃	A	586	140°C
75	OH	3- 	H	A	603	150°C
76	-(CH ₂) ₂ -OH	2-CH ₃	6-CH ₃	A	587	156°C / HCl

Table 5 : compounds prepared according to synthesis scheme G



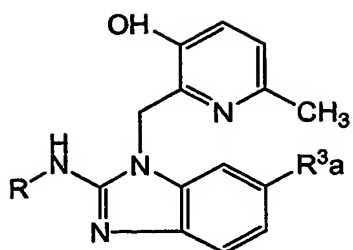
Comp. No.	R ^{3b}	R ^{2a}	R ^{3a}	R ^{2b}	Activity category	Mass (MH ⁺)	Melting point/salt
77	-CH ₃	H	-CH ₃	H	A	410	228°C
78	H	H	H	H	B	382	203°C
79	H	-CH ₃	H	-CH ₃	C	410	234°C

Table 6 :



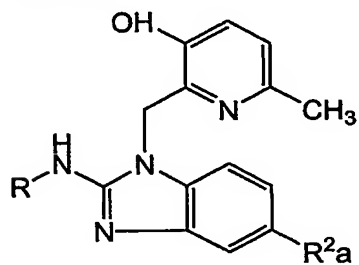
Comp. No.	n	R ^{3b}	R ^{2a}	R ^{3a}	R ^{2b}	Activity	Mass (MH ⁺)	Melting point/salt	Synthesis scheme
80	3	-CH ₃	H	-CH ₃	H	A	493	223°C	I
81	2	-CH ₃	H	-CH ₃	H	A	479	226°C	H
82	2	H	H		H	A	584	150°C	J
83	2	H	H		H	A	570	130°C	J
84	2	H	H		H	B	555	159°C	K
85	2	-CH ₃	H	H	H	B	465	238°C	H
86	2	H		H	H	B	553	225°C	K
87	2	H	H	-CH ₂ -OH	H	B	481	147°C	J
88	2	H	H		H	B	553	224°C	K
89	2	H	-CH ₃	H	-CH ₃	B	479	226°C	H

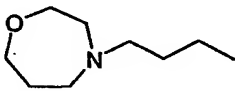
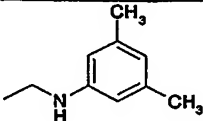
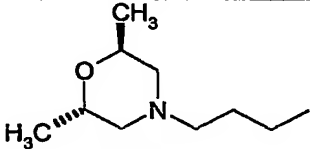
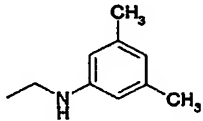
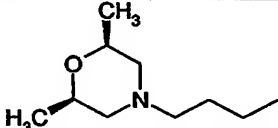
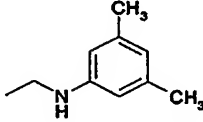
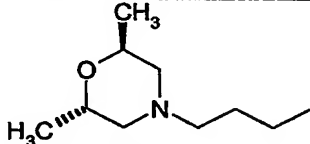
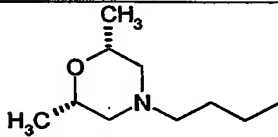
Table 7



Comp. No.	R	R ^{3a}	Activity category	Mass (MH ⁺)	Melting point/salt	Synthesis scheme
90			A	531	198°C	M
91			A	543	192°C	L
92			A	543	169°C	L
93			B	529	—	N
94		-CH ₂ -OH	B	440	199°C	L
95		H	C	410	205°C	G
96		-CH ₂ -OH	C	440	202°C	L

Table 8



Comp. No.	R	R ² a	Activity	Mass (MH ⁺)	Melting point/salt	Synthesis scheme
97			A	529	198°C	N
98			B	543	209°C	L
99			A	543	169°C	L
100		-CH ₂ -OH	C	440	212	L
101		-CH ₂ -OH	C	440	227°C	L

B. In vitro screening for activity against Respiratory Syncytial Virus.

The percent protection against cytopathology caused by viruses (antiviral activity or IC₅₀) achieved by tested compounds and their cytotoxicity (CC₅₀) are both calculated from dose-response curves. The selectivity of the antiviral effect is represented by the selectivity index (SI), calculated by dividing the CC₅₀ (cytotoxic dose for 50% of the cells) by the IC₅₀ (antiviral activity for 50 % of the cells). The tables in the above experimental part list the category to which each of the prepared compounds belong : Compounds belonging to activity category "A" have an pIC₅₀ (-log of IC₅₀ when expressed in molar units) equal to or more than 7. Compounds belonging to activity category "B" have a pIC₅₀ value between 6 and 7. Compounds belonging to activity category "C" have a pIC₅₀ value equal to or below 6.

Automated tetrazolium-based colorimetric assays were used for determination of IC₅₀ and CC₅₀ of test compounds. Flat-bottom, 96-well plastic microtiter trays were filled with 180 µl of Eagle's Basal Medium, supplemented with 5 % FCS (0% for FLU) and 20 mM Hepes buffer. Subsequently, stock solutions (7.8 x final test concentration) of compounds were added in 45 µl volumes to a series of triplicate wells so as to allow simultaneous evaluation of their effects on virus- and mock-infected cells. Five five-fold dilutions were made directly in the microtiter trays using a robot system. Untreated virus controls, and HeLa cell controls were included in each test. Approximately 100

TCID₅₀ of Respiratory Syncytial Virus was added to two of the three rows in a volume of 50 µl. The same volume of medium was added to the third row to measure the cytotoxicity of the compounds at the same concentrations as those used to measure the antiviral activity. After two hours of incubation, a suspension (4×10^5 cells/ml) of

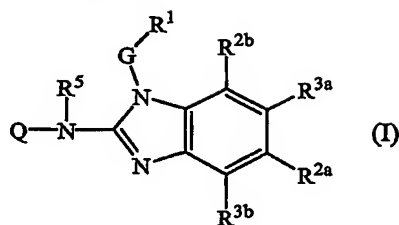
5 HeLa cells was added to all wells in a volume of 50µl. The cultures were incubated at 37°C in a 5% CO₂ atmosphere. Seven days after infection the cytotoxicity and the antiviral activity was examined spectrophotometrically. To each well of the microtiter tray, 25 µl of a solution of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added . The trays were further incubated at 37°C for 2 hours, after which

10 the medium was removed from each cup. Solubilization of the formazan crystals was achieved by adding 100 µl 2-propanol. Complete dissolution of the formazan crystals were obtained after the trays have been placed on a plate shaker for 10 min. Finally, the absorbances were read in an eight-channel computer-controlled photometer (Multiskan MCC, Flow Laboratories) at two wavelengths (540 and 690 nm). The absorbance

15 measured at 690 nm was automatically subtracted from the absorbance at 540 nm, so as to eliminate the effects of non-specific absorption.

Claims

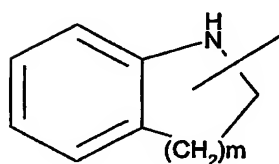
1. A compound having the formula



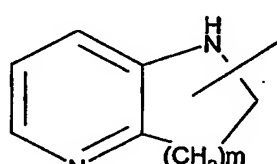
5 a prodrugs, *N*-oxide, addition salt, quaternary amine, metal complex, or a stereochemically isomeric form thereof; wherein

G is a direct bond or C₁₋₁₀alkanediyl optionally substituted with one or more substituents individually selected from the group of substituents consisting of hydroxy, C₁₋₆alkyloxy, Ar¹C₁₋₆alkyloxy, C₁₋₆alkylthio, Ar¹C₁₋₆alkylthio, HO(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n- or Ar¹C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-;

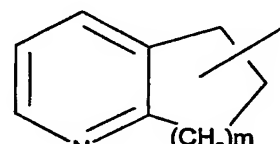
10 R¹ is Ar¹ or a monocyclic or bicyclic heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranlyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, quinolinyl, quinoxalinyl, benzofuranlyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, pyridopyridyl, naphthiridinyl, 1*H*-imidazo[4,5-*b*]pyridinyl, 3*H*-imidazo[4,5-*b*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridyl or a radical of formula



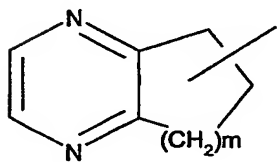
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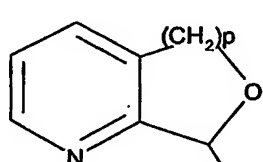
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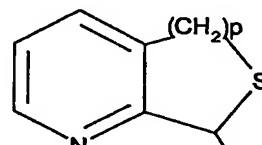
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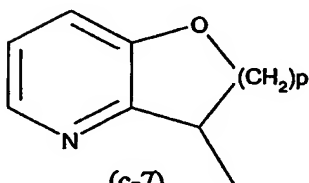
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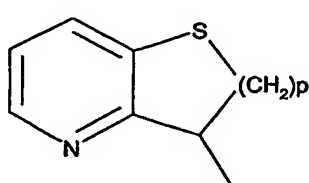
(c-5)



(c-6)



(c-7)



(c-8)

;

- wherein each of said monocyclic or bicyclic heterocycles may optionally be substituted with 1 or where possible more, such as 2, 3, 4 or 5, substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyl, Ar¹, Ar¹C₁₋₆alkyl, Ar¹C₁₋₆alkyloxy, hydroxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)amino, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, polyhaloC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, C₁₋₆alkyl-SO₂-NR^{5c}-, Ar¹-SO₂-NR^{5c}-, C₁₋₆alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C₁₋₆alkyloxy(-CH₂-CH₂-O)_n-, Ar¹C₁₋₆alkyloxy(-CH₂-CH₂-O)_n- and mono- or di(C₁₋₆alkyl)amino(-CH₂-CH₂-O)_n-;
- each n independently is 1, 2, 3 or 4;
- each m independently is 1 or 2;
- each p independently is 1 or 2;
- each t independently is 0, 1 or 2;
- Q is R⁷, pyrrolidinyl substituted with R⁷, piperidinyl substituted with R⁷ or homo-piperidinyl substituted with R⁷ wherein
- R⁷ is C₁₋₆alkyl substituted with a heterocycle or R⁷ is C₁₋₆alkyl substituted with both a radical -OR⁸ and a heterocycle, wherein said heterocycle is selected from the group consisting of oxazolidine, thiazolidine, 1-oxo-thiazolidine, 1,1-dioxothiazolidine, morpholinyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxothiomorpholinyl, hexahydrooxazepine, hexahydrothiazepine, 1-oxo-hexahydrothiazepine, 1,1-dioxo-hexahydrothiazepine; wherein each of said heterocycle may be optionally substituted with one or two substituents selected from the group consisting of C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, hydroxy, carboxyl, C₁₋₄alkyloxycarbonyl, aminocarbonyl, mono- or di(C₁₋₄alkyl)aminocarbonyl, C₁₋₄alkylcarbonylamino, aminosulfonyl and mono- or di(C₁₋₄alkyl)aminosulfonyl;
- R⁸ is hydrogen, C₁₋₆alkyl or Ar¹C₁₋₆alkyl;
- one of R^{2a} and R^{3a} is selected from halo, optionally mono- or polysubstituted C₁₋₆alkyl, optionally mono- or polysubstituted C₂₋₆alkenyl, nitro, hydroxy, Ar², N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, N(R^{4a}R^{4b})carbonyl, C₁₋₆alkyloxy, Ar²oxy, Ar²C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, or -C(=Z)Ar²; and the other one of R^{2a} and R^{3a} is hydrogen;
- wherein
- =Z is =O, =CH-C(=O)-NR^{5a}R^{5b}, =CH₂, =CH-C₁₋₆alkyl, =N-OH or =N-O-C₁₋₆alkyl; and
 - the optional substituents on C₁₋₆alkyl and C₂₋₆alkenyl can be the same or can be different relative to one another, and are each independently selected from the group of substituents consisting of hydroxy, cyano, halo, nitro, N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, Het, Ar², C₁₋₆alkyloxy, C₁₋₆alkyl-S(=O)_t, Ar²oxy,

$\text{Ar}^2\text{-S(=O)}_t$, $\text{Ar}^2\text{C}_{1-6}\text{alkyloxy}$, $\text{Ar}^2\text{C}_{1-6}\text{alkyl-S(=O)}_t$, Het-oxy , Het-S(=O)_t , $\text{HetC}_{1-6}\text{alkyloxy}$, $\text{HetC}_{1-6}\text{alkyl-S(=O)}_t$, carboxyl, $\text{C}_{1-6}\text{alkyloxycarbonyl}$ and -C(=Z)Ar^2 ;

in case R^{2a} is different from hydrogen then R^{2b} is hydrogen, $\text{C}_{1-6}\text{alkyl}$ or halogen and

5 R^{3b} is hydrogen;

in case R^{3a} is different from hydrogen then R^{3b} is hydrogen, $\text{C}_{1-6}\text{alkyl}$ or halogen and R^{2b} is hydrogen;

R^{4a} and R^{4b} can be the same or can be different relative to one another, and are each independently selected from the group of substituents consisting of hydrogen,

10 $\text{C}_{1-6}\text{alkyl}$, $\text{Ar}^2\text{C}_{1-6}\text{alkyl}$, $\text{Het-C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$, $\text{aminoC}_{1-6}\text{alkyl}$, mono- or di($\text{C}_{1-6}\text{alkyl}$) $\text{aminoC}_{1-6}\text{alkyl}$, $\text{hydroxyC}_{1-6}\text{alkyl}$, $\text{carboxylC}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyloxycarbonylC}_{1-6}\text{alkyl}$, $\text{aminocarbonylC}_{1-6}\text{alkyl}$, mono- and di($\text{C}_{1-6}\text{alkyl}$)- $\text{aminocarbonylC}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylcarbonylC}_{1-6}\text{alkyl}$, di($\text{C}_{1-6}\text{alkyloxy}$) $\text{phosphonylC}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkylcarbonyl}$, $\text{Ar}^2\text{carbonyl}$, Het-carbonyl , $\text{Ar}^2\text{C}_{1-6}\text{alkylcarbonyl}$,
15 $\text{Het-C}_{1-6}\text{alkylcarbonyl}$, $\text{C}_{1-6}\text{alkylsulfonyl}$, aminosulfonyl , mono- and di($\text{C}_{1-6}\text{alkyl}$)- aminosulfonyl , $\text{Ar}^2\text{sulfonyl}$, $\text{Ar}^2\text{C}_{1-6}\text{alkylsulfonyl}$, Ar^2 , Het , Het-sulfonyl , $\text{HetC}_{1-6}\text{alkylsulfonyl}$; ; R^5 is hydrogen or $\text{C}_{1-6}\text{alkyl}$;

R^{5a} and R^{5b} can be the same or can be different relative to one another, and are each independently hydrogen or $\text{C}_{1-6}\text{alkyl}$; or

20 R^{5a} and R^{5b} taken together may form a bivalent radical of formula $\text{-(CH}_2\text{)}_s\text{-}$ wherein s is 4 or 5;

R^{5c} and R^{5d} can be the same or can be different relative to one another, and are each independently hydrogen or $\text{C}_{1-6}\text{alkyl}$; or

25 R^{5c} and R^{5d} taken together may form a bivalent radical of formula $\text{-(CH}_2\text{)}_s\text{-}$ wherein s is 4 or 5;

Ar^1 is phenyl or phenyl substituted with 1 or more, such as 2, 3 or 4, substituents selected from halo, hydroxy, $\text{C}_{1-6}\text{alkyl}$, $\text{hydroxyC}_{1-6}\text{alkyl}$, $\text{polyhaloC}_{1-6}\text{alkyl}$, and $\text{C}_{1-6}\text{alkyloxy}$;

30 Ar^2 is phenyl, phenyl annelated with a $\text{C}_{5-7}\text{cycloalkyl}$, or phenyl substituted with 1 or more, such as 2, 3, 4 or 5, substituents selected from halo, cyano, $\text{C}_{1-6}\text{alkyl}$, $\text{Het-C}_{1-6}\text{alkyl}$, $\text{Ar}^1\text{-C}_{1-6}\text{alkyl}$, $\text{cyanoC}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, $\text{cyano-C}_{2-6}\text{alkenyl}$, Ar^1 , $\text{R}^{6b}\text{-O-}$, $\text{R}^{6b}\text{-S-}$, $\text{R}^{6c}\text{-SO-}$, $\text{R}^{6c}\text{-SO}_2\text{-}$, $\text{-N(R}^{6a}\text{R}^{6b}\text{)}$, $\text{polyhalo-C}_{1-6}\text{alkyl}$, $\text{polyhaloC}_{1-6}\text{alkyloxy}$, $\text{polyhaloC}_{1-6}\text{alkylthio}$, $\text{R}^{6c}\text{-C(=O)-}$, $\text{R}^{6b}\text{-O-C(=O)-}$, $\text{N(R}^{6a}\text{R}^{6b}\text{)-C(=O)-}$, $\text{R}^{6b}\text{-O-C}_{1-6}\text{alkyl}$, $\text{R}^{6b}\text{-S-C}_{1-6}\text{alkyl}$,
35 $\text{R}^{6c}\text{-S(=O)}_2\text{-C}_{1-6}\text{alkyl}$, $\text{N(R}^{6a}\text{R}^{6b}\text{)-C}_{1-6}\text{alkyl}$, $\text{R}^{6c}\text{-C(=O)-C}_{1-6}\text{alkyl}$, $\text{R}^{6b}\text{-O-C(=O)-C}_{1-6}\text{alkyl}$, $\text{N(R}^{6a}\text{R}^{6b}\text{)-C(=O)-C}_{1-6}\text{alkyl}$, $\text{R}^{6c}\text{-C(=O)-NR}^{6b}\text{-}$, $\text{R}^{6c}\text{-C(=O)-O-}$, $\text{R}^{6c}\text{-C(=O)-NR}^{6b}\text{-C}_{1-6}\text{alkyl}$, $\text{R}^{6c}\text{-C(=O)-O-C}_{1-6}\text{alkyl}$, $\text{N(R}^{6a}\text{R}^{6b}\text{)-S(=O)}_2\text{-}$;

- R^{6a} is hydrogen, C_{1-6} alkyl, Ar^1 , Ar^1C_{1-6} alkyl, C_{1-6} alkylcarbonyl, Ar^1 carbonyl, Ar^1C_{1-6} alkylcarbonyl, C_{1-6} alkylsulfonyl, Ar^1 sulfonyl, Ar^1C_{1-6} alkylsulfonyl, C_{1-6} alkyloxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, hydroxy C_{1-6} alkyl, Het, Het- C_{1-6} alkyl, Het-carbonyl, Het-sulfonyl, Het-
5 C_{1-6} alkylcarbonyl;
 R^{6b} is hydrogen, C_{1-6} alkyl, Ar^1 or Ar^1C_{1-6} alkyl;
 R^{6c} is C_{1-6} alkyl, Ar^1 or Ar^1C_{1-6} alkyl;
Het is a heterocycle being selected from tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidinonyl, furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl,
10 imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzodioxolyl, indolinyl, indolyl, each of said heterocycle may optionally be substituted with oxo, amino, Ar^1 , C_{1-4} alkyl, amino C_{1-4} alkyl,
15 Ar^1C_{1-4} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino.
Het is a heterocycle being selected from tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidinonyl, furanyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, piperidinyl, homopiperidinyl, piperazinyl, morpholinyl, pyridyl, pyrazinyl,
20 pyridazinyl, pyrimidinyl, tetrahydroquinolinyl, quinolinyl, isoquinolinyl, benzodioxanyl, benzodioxolyl, indolinyl, indolyl, each of said heterocycle may optionally be substituted with oxo, amino, Ar^1 , C_{1-4} alkyl, amino C_{1-4} alkyl, Ar^1C_{1-4} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino.
- 25 2. A compound as claimed in claim 1 wherein G is C_{1-10} alkanediyl.
3. A compound as claim in claim 1 or 2 wherein R^1 is pyridyl optionally substituted with 1 or 2 substituents individually selected from the group of substituents consisting of halo, hydroxy, amino, cyano, carboxyl, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkyloxy C_{1-6} alkyl, Ar^1 , Ar^1C_{1-6} alkyl, Ar^1C_{1-6} alkyloxy, hydroxy C_{1-6} alkyl, mono-or di(C_{1-6} alkyl)amino, mono-or di(C_{1-6} alkyl)amino- C_{1-6} alkyl, polyhalo C_{1-6} alkyl, C_{1-6} alkylcarbonylamino, C_{1-6} alkyl-SO₂-NR^{5c}-, Ar^1 -SO₂-NR^{5c}-, C_{1-6} alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH₂-CH₂-O)_n-, halo(-CH₂-CH₂-O)_n-, C_{1-6} alkyloxy(-CH₂-CH₂-O)_n-,
30 Ar^1C_{1-6} alkyloxy(-CH₂-CH₂-O)_n- and mono-or di(C_{1-6} alkyl)amino(-CH₂-CH₂-O)_n-.
35
4. A compound as claimed in any one of claim 1 to 3 wherein t is 2.

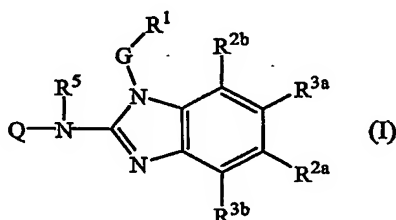
5. A compound as claimed in any one of claim 1 to 4 wherein the compound has the structure of the compound numbers 1 to 24, 26 to 77, 80 to 83, 90 to 92, 97 and 99 listed in tables 1 to 8.
- 5 6. A compound as claimed in any one of claims 1 to 5 for use as a medicine.
7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as described in any one of claims 1 to 5.

ABSTRACT

MORPHOLINYL CONTAINING BENZIMIDAZOLES AS INHIBITORS OF
RESPIRATORY SYNCYTIAL VIRUS REPLICATION

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The present invention concerns morpholinyl containing benzimidazoles having inhibitory activity on the replication of the respiratory syncytial virus and having the formula



- 10 a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex or stereochemically isomeric form thereof wherein G is a direct bond or optionally substituted C₁₋₁₀alkanediyl; R¹ is Ar¹ or a monocyclic or bicyclic heterocycle
- Q is R⁷, pyrrolidinyl substituted with R⁷, piperidinyl substituted with R⁷ or homopiperidinyl substituted with R⁷; one of R^{2a} and R^{3a} is selected from halo,
- 15 optionally mono- or polysubstituted C₁₋₆alkyl, optionally mono- or polysubstituted C₂₋₆alkenyl, nitro, hydroxy, Ar², N(R^{4a}R^{4b}), N(R^{4a}R^{4b})sulfonyl, N(R^{4a}R^{4b})carbonyl, C₁₋₆alkyloxy, Ar²oxy, Ar²C₁₋₆alkyloxy, carboxyl, C₁₋₆alkyloxycarbonyl, or -C(=Z)Ar²; and the other one of R^{2a} and R^{3a} is hydrogen; in case R^{2a} is different from hydrogen then R^{2b} is hydrogen, C₁₋₆alkyl or halogen and R^{3b} is hydrogen; in case R^{3a} is different
- 20 from hydrogen then R^{3b} is hydrogen, C₁₋₆alkyl or halogen and R^{2b} is hydrogen. It further concerns their preparation and compositions comprising them, as well as their use as a medicine.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP04/053620

International filing date: 20 December 2004 (20.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 04105312.5
Filing date: 26 October 2004 (26.10.2004)

Date of receipt at the International Bureau: 14 March 2005 (14.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

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